Title: Management of thymoma associated autoimmune pure red cell aplasia: case report and systematic review of the literature.

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Highlights:

- Thymectomy is the most effective therapy for thymoma associated PRCA
- If PRCA persists after thymectomy, immunomodulatory therapy particularly cyclosporine, is effective.

Abstract

Pure red cell aplasia (PRCA) is a rare paraneoplastic syndrome observed in 2-5% of thymomas. Literature reports great variability in its management. Based on an illustrative clinical case, we present a systematic literature review whose main objective is to evaluate the therapeutic management of PRCA. The literature search was performed based on the PICO method in the Medline and Scopus databases. The reference clinical case concerns a 51-year-old woman with stage IVa thymoma. After initial response to chemotherapy, a locoregional progression occurred with PRCA development that responded favorably under second line chemotherapy. The patient finally died in a context of bicytopenia with febrile neutropenia. The systematic review covers 132 articles published between 1950 and 2019. Thymectomy alone or in combination with other therapies showed a 31% complete remission (CR) rate for PRCA of, whereas none was reported with anti-tumor treatments without thymectomy. Among immunomodulatory therapies, cyclosporin gave the highest percentage of CR (74%). Finally, the combination of thymectomy and immunomodulatory treatments showed a CR rate of 45%. Thymectomy appeared to be the most effective anti-tumor treatment for PRCA. Immunomodulatory therapies, particularly cyclosporine, are shown effective, but the risk of infectious complications must be considered. The optimal place of anti-tumor and immunomodulatory therapies against PRCA has yet to be determined.

Keywords: Pure red cell aplasia, erythroblastopenia, thymoma, thymic carcinoma, systematic review, clinical case.

1. Introduction

Thymoma associated pure red cell aplasia (PRCA) is a rare paraneoplastic syndrome [1, 2]. Several etiological hypotheses are formulated: role of self-reactive T-cells, clonal lymphocyte disorder and anti-erythroblast antibodies [3-5]. Classical symptoms of anemia such as fatigue, weakness, pallor or dyspnea may reveal PRCA. PRCA may be found at time of thymoma diagnosis or may develop several years later [6]. It is usually a non-regenerative, normocytic or sometimes macrocytic anemia. Bone marrow examination generally shows a normal abundance of myeloid cells and megakaryocytes contrasting with the complete absence of erythroblasts [5, 7]. Published data are essentially case reports with a great variability concerning the time of onset of aplasia, its evolution and management [7, 8]. Therapeutic options consist of supportive treatments (iterative transfusions, erythropoietin [EPO]), Immunosuppressive/immunomodulatory treatments (corticosteroid therapy, cyclosporin...) or oncological treatments (thymectomy, radiotherapy, chemotherapy) [8, 9].

Based on an illustrative clinical case, we conducted a systematic review of the literature on the management of thymoma-associated PRCA. Its main objective is to evaluate the impact of thymoma treatment on the therapeutic management of PRCA. The Jules Bordet Institute's ethics committee approved the research protocol on 6/12/2018. (Reference CE 2921).

2. Clinical Case:

A 51-year-old woman was referred for management of a stage IVa B1 thymoma, discovered incidentally on a chest X-ray. Her past medical history is limited to an operated leiomyosarcoma two years before. She neither smoked nor drank and was taking only and vitamin D and hormone replacement therapy for menopause.

Initial lab tests were normal including a complete blood count. The tumor was initially unresectable (extensive pleural involvement). Chemotherapy combining cisplatin, adriamycin, cyclophosphamide was started. After the third cycle, the patient presented a mild regenerative anemia with hemoglobin (Hb) level at 10.2 g/dl which was attributed to chemotherapy. She received a subcutaneous injection of EPO (epoetin alpha 40000UI/week). After the fourth cycle of chemotherapy, a morphological and metabolic response of the thymoma was demonstrated. Pleuro-pneumectomy was denied by the patient. She was later hospitalized for a cerebral hemorrhage secondary to central venous thrombosis, four weeks after the first EPO injection. The chemotherapy and EPO were stopped.

Six months later, the disease slowly progressed essentially at the pleural level. There was no anemia and no clinical impact for 9 months. The patient refused to resume chemotherapy. Nineteen months after diagnosis, she was admitted for dyspnea (grade 3 according to mMRC) associated with tinnitus and palpitations. The biology showed normocytic anemia at 6.2 g/dl with reticulocytopenia. There was no iron, vitamin B9 or B12 deficiency (Table 1)**.** Serologies for parvovirus B19 are negative. The EPO level was high. The fecal occult blood tests were negative, and a gastroscopy revealed mild chronic gastritis. Subsequently, a bone marrow biopsy showed aplasia of the erythroid lineage without excess blasts, while the myeloid and megakaryocyte lineages remained within norms. After collegial discussion with the hematologists, the diagnosis of PRCA secondary to the thymoma was retained [7]; a possible responsibility of erythropoietin administration was considered unlikely. The patient was transfused with red blood cells several times in view of the symptoms (Figure 1).

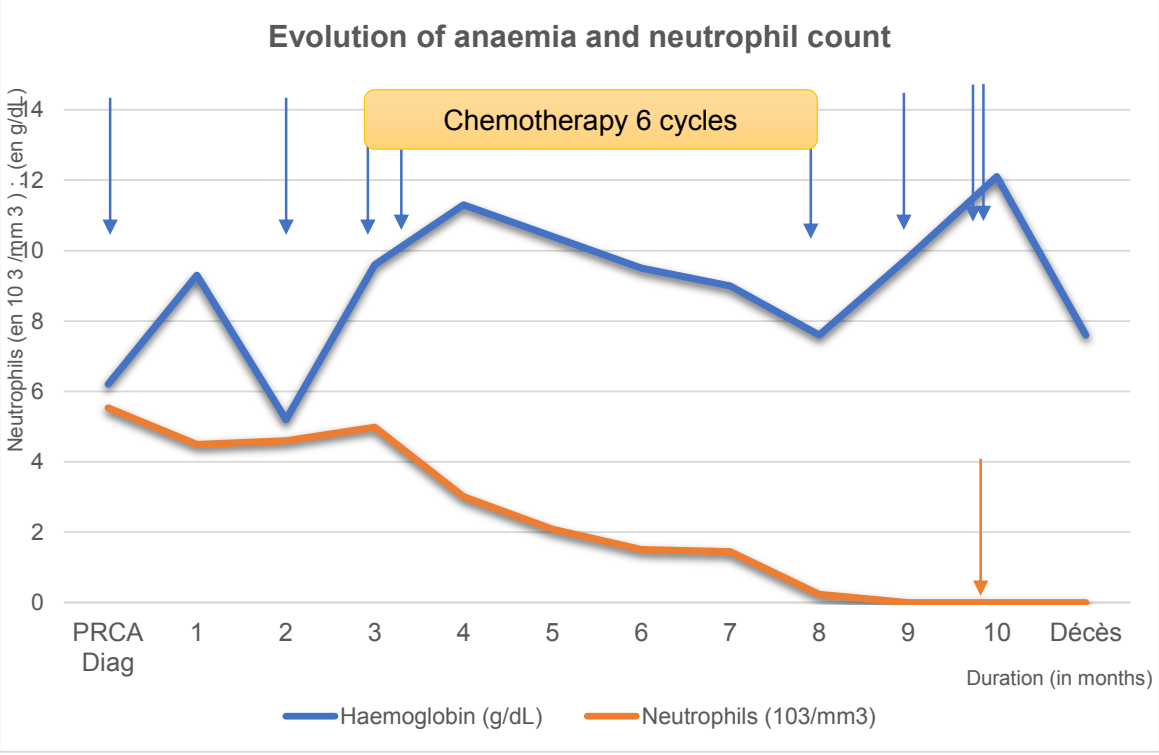
Three months later, the patient agreed to resume cisplatin-adriamycin-cyclophosphamide. In parallel with tumor regression, the patient became transfusion-independent for 5 months and partially controlled anemia between 9 and 11 g/dl during chemotherapy cycles 2 to 5. After the latter cycle, the patient had to be transfused again due to

Table 1: General laboratory analyses

Laboratory	At Diagnostic of PRCA	At bicytopenia	Reference values
Hemoglobin	6.2	9.8	12-16 g/dl
MCV	94	94	80-100 fL
Reticulocytes	$4x10^3$	$45.8x10^3$	$22.5\text{-}147x10^3/\mu L$
Haptoglobin	162	/	30-200 mg/dL
Ferritin	519	2060	30-350 µg/L
Serum iron	182	18	50-170 µg/dL
Transferrin	225	116	250-380 mg/dL
Tf saturation	58	11	15-50%
Vitamin B9	7.5	12.5	> 4.6 µg/L
Vitamin B12	388	659	197-771 ng/L
CRP	38	175.6	< 10mg/L
Erythropoietin	2453	/	1-9 U/L
Leukocytes	12280	1790	3500-11000/µL
Neutrophils	$5.53x10^3$	0	1.5-6.7x10/µL
Monocytes	$0.25x10^3$	$0.07x10^3$	$0.2\text{-}1x10^3/\mu L$
Basophiles	0	0	$<0.1x10^3/\mu L$
Eosinophils	0	0	$<0.4x10^3/\mu L$
Lymphocytes	$6.51x10^3$	$1.72x10^3$	$1.2\text{-}3.5x10^3/\mu L$
Platelets	$345x10^3$	$301x10^3$	$150\text{-}440x10^3$/microL

Abbreviations: CRP, C reactive protein; MCV, mean corpuscular volume; Tf , transferrin.

Figure 1: Clinical case graph on the evolution of anemia and neutrophil count over time



Blue arrow = transfusion concentrated red blood cells; Orange arrow = filgrastim injection.

Abbreviations: Diag, diagnosis; Hb, hemoglobin; PMN, neutrophils.

recurrence of anemia symptoms. At that time, it was difficult to distinguish whether this recurrence is secondary to the chemotherapy or to the PRCA relapse.

At the end of the 6th course of chemotherapy, the patient was hospitalized for febrile neutropenia. There was no tumor recurrence at chest scanner. The blood count showed a persistence of anemia at 9.8 g/dl and a complete absence of neutrophils. A new bone marrow aspiration showed a hypocellular bone marrow containing only a few megakaryocytes. A bone marrow biopsy showed no evidence of leukemia, thymoma invasion or macrophage activation syndrome (MAS). Under antibiotic therapy, the patient improved progressively. She received red blood cells transfusions, and 6 injections of filgrastim with no effect on neutropenia. Three weeks later, the patient presented a new episode of febrile neutropenia with zona and positive blood cultures for *Serratia marcescens*. Despite broad-spectrum antibiotic and improvement of skin lesions, the patient deteriorate continuously. A new marrow aspiration showed low cellularity with almost exclusive presence of T-lymphocytes. A macrophagic activation syndrome was suspected in the face of an elevation of the CD25a marker, hyperferritinemia, hypertriglyceridemia, bicytopenia and pyrexia [10]. This bicytopenia could also correspond to a paraneoplastic syndrome as a progression of the thymoma was seen. The patient denied additional investigations and treatment with etoposide-dexamethasone. Palliatives cares were provided. The patient died in a context of multi-organ failure with persistent bicytopenia, blood transfusions dependency and candidemia (*C. tropicalis*), despite caspofungin and broad-spectrum antibiotics. The family refused an autopsy.

3. Materials and methods

We performed a systematic review of the literature on autoimmune PRCA associated with thymoma. The literature search was conducted using the PICO (Population, Intervention,

Comparator, Outcome) technique for the formulation of the research equation: P = Patients with PRCA secondary to a thymoma; I = anti-tumor treatment (systemic, radiotherapy, surgery); C = iterative transfusions of red blood cells; O = resolution of anemia.

The corresponding research criteria of "P" were translated into MeSH terms, and free-text keywords that were searched for in title and abstracts. An experienced medical scientific librarian performed literature search in December 2019 using the Medline database via the OvidSP interface. This research equation was adapted for use in the Scopus database. A first selection based on the title and the abstract content was made by independent double reading by two authors (BL and TB). Articles selected by at least one of the two readers were retained for full reading.

Selections criteria were: language accessible to the reader (French, English, Dutch, Spanish, Italian), clinical case or case series, prospective or retrospective study, systematic review or meta-analysis, evaluation of the therapeutic management of PRCA associated with thymoma and individual case data available. The research was supplemented by screening the references of the selected articles. There was no selection based on the year of publication.

The following variables were collected from each eligible article: age, sex, performance status, thymoma characteristics (Histologic and stage classifications,), thymoma treatment (surgery, chemotherapy, radiotherapy, multimodal) and response to treatment, time of PRCA onset (at diagnosis of the thymoma or the current therapeutic line), assessment and biological characteristics of anemia (iron, B9, B12, parvovirus B19, Hb level, reticulocytes, EPO, myelogram…), other blood cell dysfunction (platelets, white blood cells), other paraneoplastic syndrome (myasthenia gravis, Good's syndrome ...), PRCA treatment and its response, evolution of the thymoma compared to PRCA, eventual death and its etiology. The PRCA evolution on treatment was arbitrarily classified into three categories: complete remission (CR)

for return to normal hemoglobinemia, partial remission (PR) for persisting anemia not requiring transfusion as opposed to transfusion dependence of persistent disease (PD).

Descriptive statistics are limited to mean and median calculations performed with "Excel" software**.**

4. Results

Overall (figure 2), 136 articles were retained, including 119 case reports and 17 case series, published between 1950 and 2018. Three case series were excluded: a Japanese national cohort [11], a French observational study [12] and an American cohort [13] because they overlapped with selected clinical cases described more precisely in other publications. WE found one old systematic review [14]; we retained its illustrative clinical case, but the other bibliographical references cannot be retrieved.

For each clinical case, all the therapeutic lines were evaluated individually (table 2 in appendix). PRCA diagnoses were reported by identifying the time of occurrence in relation to the therapeutic line and the status of the thymic disease. Overall, there were 185 clinical cases corresponding to 312 therapeutic lines.

PRCA occurred most frequently at thymoma diagnosis (111/185). Sixty-two PRCA occurred after a median thymic disease duration of 36 months. In 12 cases, PRCA was diagnosed before thymoma discovery.

Table 3 summarizes the response of PRCA according to the applied treatment, divided into three groups (anti-tumor treatment, immune-mediated treatment, or a combination of the two approaches). Overall, tumor treatments resulted in 29.6% CR. Thymectomy alone or in combination with other therapies showed a 31.5% CR rate, whereas chemotherapy and/or radiotherapy without thymectomy showed quite none. Treatments acting on the immune system

Figure 2: Flow chart

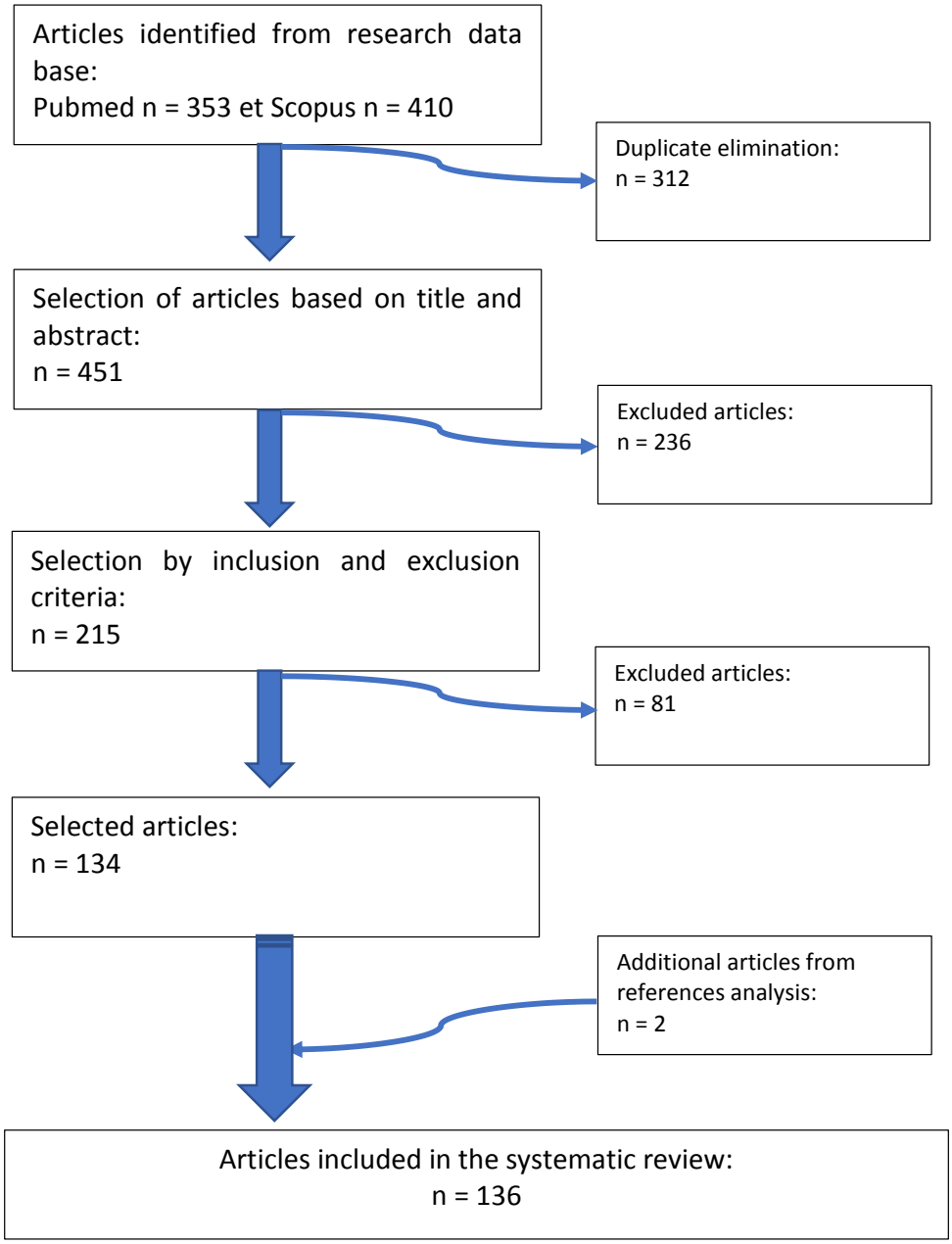


Table 3: PRCA responses in function of the treatment applied

Therapeutic sequence	CR	PR	PD
Anti-tumor treatment:			
- **Thymectomy**	**23**	**6**	**50**
- **Thymectomy + Chemotherapy**	**2**	**-**	**1**
- **Thymectomy + Radiotherapy**	**4**	**1**	**4**
- **Thymectomy + Chemotherapy +**	**-**	**-**	**1**
Radiotherapy	**-**	**1**	**3**
- **Chemotherapy**	**-**	**-**	**1**
- **Radiotherapy**	**-**	**-**	**1**
- **Chemotherapy + Radiotherapy**	**29**	**8**	**61**
- **Total**			
Treatments acting on the immune system:			
- **Corticosteroids**	25	5	31
- **Cyclosporin**	23	3	5
- **Cyclophosphamide**	2	-	2
- **Azathioprine**	1	-	2
- **Others IST unspecified**	6	-	2
- **Other monotherapy***	8	5	14
- **Corticoids + Cyclophosphamide**	9	1	7
- **Corticoids + Cyclosporin**	3	-	4
- **Others combinations**	4	4	15
- **Total**	81	18	82
Combination of anti-tumor treatment and treatments acting on the immune system:			
- **Thymectomy + Corticoids**	6	4	2
- **Thymectomy + Combination IST**	3	1	1
- **Thymectomy + Corticoids + Cyclosporin**	1	-	-
- **Chemotherapy + Combination IST**	2	-	2
- **Chemotherapy + Radiotherapy + Corticoids**	-	-	1
- **Radiotherapy + Combination IST**	1	4	1
- **Total**	13	9	7

Numbers are presenting the number of patients in each category

*adrenocorticotropic hormone; androgens; rituximab; splenectomy; anti-thymocytes globulins; immunoglobulins; bone marrow allograft; plasmapherese.

showed a CR rate of 45%, 74% with cyclosporine compared to 41% after corticosteroids. Corticosteroid-cyclophosphamide and corticosteroid-cyclosporin combinations have CR rates of 53% and 43%. Combination treatments of anti-tumor treatment and treatments acting on the immune system have a CR rate of 45%. Combinations including thymectomy had a 56% CR rate versus 27% CR for combinations without thymectomy.

When PRCA persisted after thymectomy (Table 4), remission was essentially achieved with immunomodulatory treatments and overall CR rate of approximately 50% regardless of the treatment line. CR of PRCA was associated in 70% of cases with thymic CR while persistent PRCA (PD) does not appear to be associated with progressing thymoma.

PRCA response according to Masaoka stage could be assessed in 46 cases; there were 15 CR out of 29 stage I or II and 9 CR out of 17 stage III and IV thymoma ($p = 0.94$). Also, we did not observe any influence of histology with 10 CR out of 26 cases for types A, AB and B1 and 7 CR out of 11 cases in types B2 and B3 ($p = 0.15$).

The median duration of PRCA CR was 18 months after immunomodulatory treatment versus 15 months after anti-tumor treatment alone or in combination with an IST treatment. There was no effect of PRCA onset and CR, with 60% versus 55% CR when PRCA occurred at thymoma diagnosis or during the course of the disease. Five cases of spontaneous remission were observed and an average of 1.7 PRCA flare-ups (persistence/worsening despite treatment) were identified per patient.

Twenty-one relapses of PRCA were identified including 5 in parallel to the thymic relapse. There were 58 reported deaths. Eight are directly attributable to thymic progression. The majority (n=36) are secondary to PRCA treatment with infectious origin (n=25 including 20 on immunomodulatory therapy) and 6 in the context of systemic hemosiderosis.

Table 4: PRCA rescue therapy and responses in case of PRCA persistence post-thymectomy

2nd line (N=44)*		3rd line (N=17)		More than 3 lines (N=11)	
Chemotherapy	1 PD	Allograft	1 CR 1 PR	Corticoids	2 CR 1 PD
Corticosteroids	7 CR 8 PD	Corticosteroids	2 CR 1 PD	Cyclosporine	2 CR 1PD
Cyclosporin	3 CR 2 PR	Cyclosporin	3 CR	IgIV	1 PR
CPA	2 PD	IgIV	1 PD	Others IST	1 CR
Azathioprine	1 CR	ATG	1 PD	Combinations	2PD
Androgens	1 CR 2 PD	Androgens	1 PD	ACTH	1CR
Others IST	3 CR	Splenectomy	1 CR 1PD		
Combinations	6 CR 1PR 7PD	Combinations	2 CR 2PD		

5. Discussion

We present an illustrative clinical case of PRCA diagnosed during the course of stage IVA thymoma, with parallel PRCA and thymoma partial remission during chemotherapy. A systematic review was conducted in order assessing the best therapeutic option for controlling this rare paraneoplastic syndrome.

Thymectomy is the therapeutic cornerstone for thymoma, whatever alone or in a multimodal approach. It is also the main antitumoral and the most effective therapeutic option for PRCA, essentially for the first line care of PRCA. Only six documented cases were treated only with chemotherapy and/or radiotherapy with only one reported PR. Our clinical case corresponds to a very rare situation of PRCA partial response with chemotherapy alone. The results from the systematic review are supporting the role of thymectomy as a key factor for controlling PRCA [15, 16]. Due to the scarcity of the disease, there is no controlled trial comparing therapeutic attitude "with" versus "without" thymectomy. In the present setting, data with thymectomy may be biased by selection of less aggressive thymomas, particularly stages I and II and type A or AB. However, we did not find a difference in the control rate of PRCA

depending on Masaoka stage or histological subtypes (A, AB, B1 versus B2 and B3), yet if the value of this analysis is limited by the low number of published cases and the changes in classifications over time [17].

Treatments with immunomodulatory action, mainly cyclosporin and corticosteroids demonstrated in this systematic review their interest in the management of PRCA, whatever in first-line or in case or PRCA recurrence. Japanese [11] and American [13] national cohorts reported similar figures. These results are in contradiction with a French observational study [12] in which corticosteroid were most effective. Finally, combination therapies (anti-tumor + IST) do not show a better efficacy in terms of CR rate than immunomodulatory treatments but do expose to an increased risk of side effects, whereas an anti-tumor treatment alone may be sufficient in one third of cases.

The PRCA onset is generally at thymoma diagnosis while one-third occurred later. Our case occurred concomitantly with a thymic relapse. Other differential diagnoses were reasonably excluded. PRCA secondary to anti-EPO antibodies is not consistent with high EPO level and PR under chemotherapy [18]. Thymoma bone marrow infiltration or post-anthracycline leukemia were excluded by multiple bone marrow aspiration and biopsy. Infections as parvovirus B19 were negative and the discrete chronic gastritis did not explain such anemia. It is also questionable whether the anemia (6 months prior to PRCA) attributed to the first cycle of chemotherapy is not already representative for the start of PRCA but this anemia responded to EPO and did not recur when chemotherapy was stopped.

The terminal course is marked by the development of bicytopenia (neutropenia-anemia), for which the diagnosis of MAS was suggested due to the presence of both biological (bicytopenia, hypertriglyceridemia, hyperferritinemia, CD25 increased) and clinical (pyrexia and skin lesions) criteria. The H-Score is 169 corresponding to a probability of 78% [10]. The etiology of MAS could be active thymoma or infection. Myelogram ruled out leukemia or

medullar invasion. Nevertheless, the low cellularity should suggest a relapse of PRCA coupled with paraneoplastic neutropenia. Approximately 10 cases of white blood cell aplasia secondary to thymoma have been described and could be treated by thymectomy or immunosuppression [19]. There were also five cases in the French cohort [12]. No association of PRCA and agranulocytosis was found in the literature. In our systematic review, there were only two cases of leukopenia associated with PRCA, but they did not show neutropenia. However, the association PRCA with amegacaryocyte thrombocytopenia was described and there are more than ten cases in our systematic review. Finally, two cases of pancytopenia were reported but without neutropenia. A systematic review of the few cases of pancytopenia associated with thymomas was suggesting a therapeutic role for immunosuppressive drugs [20].

In our systematic review, we observed that complications secondary to PRCA treatment are representing the largest cause of death, particularly by infection secondary to immunosuppression. Other authors found the same findings with cyclosporin and recommended careful monitoring of patients undergoing IST treatment [11]. The French review even suggests the use of rituximab to avoid immunosuppression based on their two cases of CR out of 4 treated [12]. However, there was only one case treated with rituximab in our review showing PR.

This systematic review has some limitations. The data reported in the selected clinical cases are very heterogeneous, particularly with regard to thymic characteristics (stage and type, duration and type of treatment, type of response), PRCA (diagnostic means, duration and type of treatment, duration and type of response) and patient follow-up (duration of follow-up, possible cause of death). Criteria for PRCA remission are based on the normal hemoglobin level and independence from transfusion but do not take into account the duration or decrease in frequency of transfusion. We defined arbitrarily these criteria in the absence of literature consensus. Corticosteroid was considered by default as treatment for PRCA except when

explicitly described as an anti-tumor therapy. We did not select foreign language articles that were inaccessible to readers: sixty articles in Japanese, four in German, two in Korean, two in Chinese, one in Danish and one in Russian were excluded while some Japanese articles translated into English from other journals were retained. Finally, the analysis by therapeutic line does not reveal the influence of previous therapies on the final PRCA control.

6. Conclusion:

In this systematic review, thymectomy appears to be the most effective anti-tumor therapy for PRCA associated thymoma. Other anti-tumor treatments may induce partial remissions, but no case of complete remission was reported. If PRCA persists after thymectomy, immunomodulatory therapy should be considered with cyclosporin having the best CR, taking into account the risk of infectious complications. The respective place of anti-tumor and immunomodulatory treatments for PRCA, or their combination must be validated in prospective clinical studies.

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- If PRCA persists after thymectomy, immunomodulatory therapy particularly cyclosporine, is effective.

Abstract

Pure red cell aplasia (PRCA) is a rare paraneoplastic syndrome observed in 2-5% of thymomas. Literature reports great variability in its management. Based on an illustrative clinical case, we present a systematic literature review whose main objective is to evaluate the therapeutic management of PRCA. The literature search was performed based on the PICO method in the Medline and Scopus databases. The reference clinical case concerns a 51-year-old woman with stage IVa thymoma. After initial response to chemotherapy, a locoregional progression occurred with PRCA development that responded favorably under second line chemotherapy. The patient finally died in a context of bicytopenia with febrile neutropenia. The systematic review covers 132 articles published between 1950 and 2019. Thymectomy alone or in combination with other therapies showed a 31% complete remission (CR) rate for PRCA of, whereas none was reported with anti-tumor treatments without thymectomy. Among immunomodulatory therapies, cyclosporin gave the highest percentage of CR (74%). Finally, the combination of thymectomy and immunomodulatory treatments showed a CR rate of 45%. Thymectomy appeared to be the most effective anti-tumor treatment for PRCA. Immunomodulatory therapies, particularly cyclosporine, are shown effective, but the risk of infectious complications must be considered. The optimal place of anti-tumor and immunomodulatory therapies against PRCA has yet to be determined.

Keywords: Pure red cell aplasia, erythroblastopenia, thymoma, thymic carcinoma, systematic review, clinical case.

1. Introduction

Thymoma associated pure red cell aplasia (PRCA) is a rare disorder linked to thymoma that could be an autoimmune phenomenon, as myasthenia [1, 2]. Some etiologies are proposed: role of self-reactive T-cells, clonal lymphocyte disorder and anti-erythroblast antibodies [3-5]. Classical symptoms of anemia such as fatigue, weakness, pallor or dyspnea may reveal PRCA. PRCA may be found at time of thymoma diagnosis or may develop several years later [6]. It is usually a non-regenerative, normocytic, or sometimes macrocytic anemia. Bone marrow examination generally shows a normal abundance of myeloid cells and megakaryocytes contrasting with the complete absence of erythroblasts [5, 7]. Published data are essentially case reports with a great variability concerning the time of onset of aplasia, its evolution and management [7, 8]. Therapeutic options consist of supportive treatments (iterative transfusions, erythropoietin [EPO]), Immunosuppressive/immunomodulatory treatments (corticosteroid therapy, cyclosporin...) or oncological treatments (thymectomy, radiotherapy, chemotherapy) [8, 9].

Based on an illustrative clinical case, we conducted a systematic review of the literature on the management of thymoma-associated PRCA. Its main objective is to evaluate the impact of thymoma treatment on the therapeutic management of PRCA. The Jules Bordet Institute's ethics committee approved the research protocol on 6/12/2018. (Reference CE 2921).

2. Clinical Case:

A 51-year-old woman was referred for management of a stage IVa B1 thymoma, discovered incidentally on a chest X-ray. Her past medical history is limited to an operated leiomyosarcoma two years before. She neither smoked nor drank and was taking only vitamin D and hormone replacement therapy for menopause.

Initial lab tests were normal including a complete blood count. The tumor was initially unresectable (extensive pleural involvement). Chemotherapy combining cisplatin, adriamycin, cyclophosphamide was started. After the third cycle, the patient presented a mild regenerative anemia with hemoglobin (Hb) level at 10.2 g/dl which was attributed to chemotherapy. She received a subcutaneous injection of EPO (epoetin alpha 40000UI/week). After the fourth cycle of chemotherapy, a morphological and metabolic response of the thymoma was demonstrated. Pleuro-pneumectomy was denied by the patient. She was later hospitalized for a cerebral hemorrhage secondary to central venous thrombosis, four weeks after the first EPO injection. The chemotherapy and EPO were stopped.

Six months later, the disease slowly progressed essentially at the pleural level. There was no anemia and no clinical impact for 9 months. The patient refused to resume chemotherapy. Nineteen months after diagnosis, she was admitted for dyspnea (grade 3 according to modified Medical Research Council dyspnea scale) associated with tinnitus and palpitations. The biology showed normocytic anemia at 6.2 g/dl with reticulocytopenia. There was no iron, vitamin B9 or B12 deficiency (Table 1)**.** Serologies for parvovirus B19 were negative. The EPO level was high. The fecal occult blood tests were negative, and a gastroscopy revealed mild chronic gastritis. Subsequently, a bone marrow biopsy showed aplasia of the erythroid lineage without excess blasts, while the myeloid and megakaryocyte lineages remained within norms. The OGATA score was 0, excluding myelodysplasia. Lymphocyte B were absent and the CD4/CD8 ratio was reduced. After collegial discussion with the hematologists, the diagnosis of PRCA secondary to the thymoma was retained [7]; a possible responsibility of erythropoietin administration was considered unlikely. The patient was transfused with red blood cells several times in view of the symptoms (Figure 1).

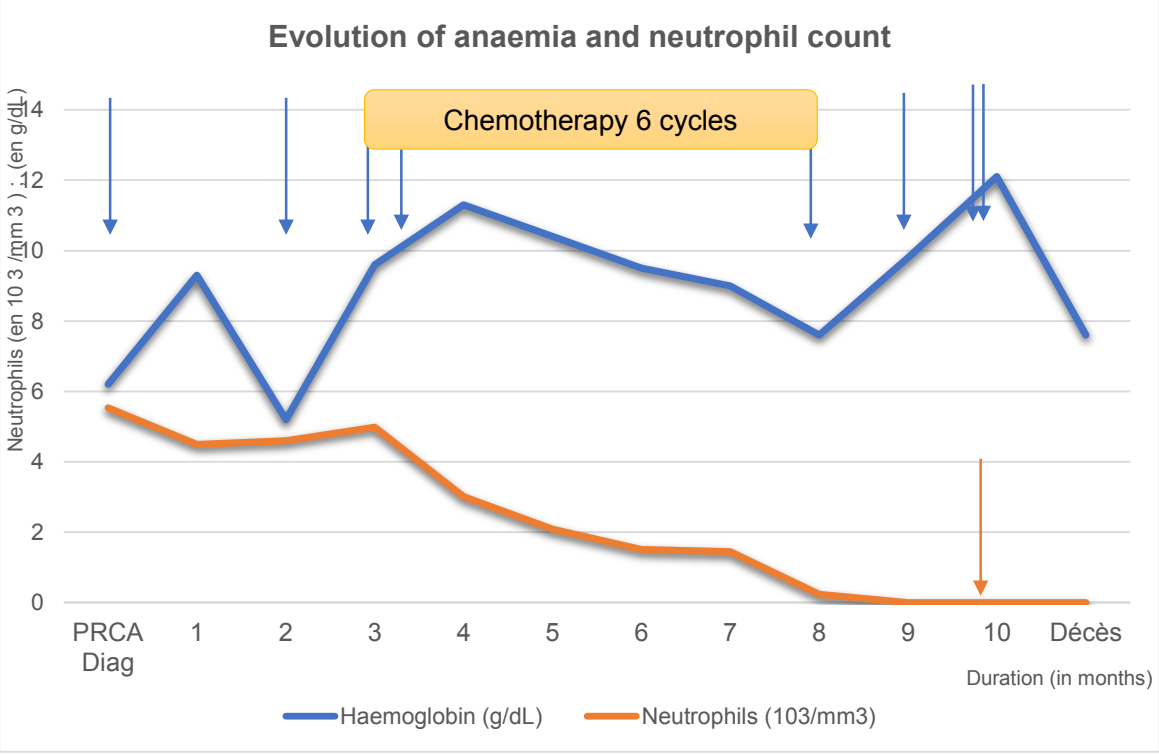
Three months later, the patient agreed to resume cisplatin-adriamycin-cyclophosphamide. In parallel with tumor regression, the patient became transfusion-

Table 1: General laboratory analyses

Laboratory	At Diagnostic of PRCA	At bicytopenia	Reference values
Hemoglobin	6.2	9.8	12-16 g/dl
MCV	94	94	80-100 fL
Reticulocytes	$4x10^3$	$45.8x10^3$	$22.5\text{-}147x10^3/\mu L$
Haptoglobin	162	/	30-200 mg/dL
Ferritin	519	2060	30-350 µg/L
Serum iron	182	18	50-170 µg/dL
Transferrin	225	116	250-380 mg/dL
Tf saturation	58	11	15-50%
Vitamin B9	7.5	12.5	> 4.6 µg/L
Vitamin B12	388	659	197-771 ng/L
CRP	38	175.6	< 10mg/L
Erythropoietin	2453	/	1-9 U/L
Leukocytes	12280	1790	3500-11000/µL
Neutrophils	$5.53x10^3$	0	1.5-6.7x10/µL
Monocytes	$0.25x10^3$	$0.07x10^3$	$0.2\text{-}1x10^3/\mu L$
Basophiles	0	0	$<0.1x10^3/\mu L$
Eosinophils	0	0	$<0.4x10^3/\mu L$
Lymphocytes	$6.51x10^3$	$1.72x10^3$	$1.2\text{-}3.5x10^3/\mu L$
Platelets	$345x10^3$	$301x10^3$	$150\text{-}440x10^3$/microL

Abbreviations: CRP, C reactive protein; MCV, mean corpuscular volume; Tf , transferrin.

Figure 1: Clinical case graph on the evolution of anemia and neutrophil count over time



Blue arrow = transfusion concentrated red blood cells; Orange arrow = filgrastim injection.

Abbreviations: Diag, diagnosis; Hb, hemoglobin; PMN, neutrophils.

independent for 5 months and partially controlled anemia between 9 and 11 g/dl during chemotherapy cycles 2 to 5. After the latter cycle, the patient had to be transfused again due to recurrence of anemia symptoms. At that time, it was difficult to distinguish whether this recurrence is secondary to the chemotherapy or to the PRCA relapse.

At the end of the 6th course of chemotherapy (Adriamycin cumulative dose 316 mg/m²), the patient was hospitalized for febrile neutropenia. There was no tumor recurrence at chest scanner. The blood count showed a persistence of anemia at 9.8 g/dl and a complete absence of neutrophils. A new bone marrow aspiration showed a hypocellular bone marrow containing only a few megakaryocytes. There were no abnormal cells, no plasmocytes and a normal CD4/CD8 ratio without B lymphocytes. A bone marrow biopsy showed no evidence of leukemia, thymoma invasion or macrophage activation syndrome (MAS). Under antibiotic therapy, the patient improved progressively. She received red blood cells transfusions, and 6 injections of filgrastim with no effect on neutropenia. Three weeks later, the patient presented a new episode of febrile neutropenia with positive blood cultures for *Serratia marcescens*. Clinically, the patient presents a vesicular rash suspicious of zona and we start Aciclovir. The patient never presented mucosal lesions, making a Steven Johnson syndrome unlikely. Despite a quick improvement of skin lesions and broad-spectrum antibiotic, the patient deteriorate continuously. A new marrow aspiration showed low cellularity with almost exclusive presence of T-lymphocytes (97%) without phenotypic abnormalities. A macrophagic activation syndrome was suspected in the face of an elevation of the CD25a marker, hyperferritinemia, hypertriglyceridemia, bicytopenia and pyrexia [10] but no hemagophagocytosis was seen at bone marrow aspirate. This bicytopenia could also correspond to a paraneoplastic syndrome as a progression of the thymoma was seen. The patient denied additional investigations and treatment with etoposide-dexamethasone. Palliatives cares were provided. The patient died in a context of multi-organ failure with persistent bicytopenia, blood transfusions dependency and

candidemia (*C. tropicalis*), despite caspofungin and broad-spectrum antibiotics. The family refused an autopsy.

3. Materials and methods

We performed a systematic review of the literature on autoimmune PRCA associated with thymoma. The literature search was conducted using the PICO (Population, Intervention, Comparator, Outcome) technique for the formulation of the research equation: P = Patients with PRCA secondary to a thymoma; I = anti-tumor treatment (systemic, radiotherapy, surgery); C = iterative transfusions of red blood cells; O = resolution of anemia.

The corresponding research criteria of "P" were translated into MeSH terms, and free-text keywords that were searched for in title and abstracts. An experienced medical scientific librarian performed literature search in December 2019 using the Medline database via the OvidSP interface. This research equation was adapted for use in the Scopus database. A first selection based on the title and the abstract content was made by independent double reading by two authors (BL and TB). Articles selected by at least one of the two readers were retained for full reading.

Selections criteria were: language accessible to the reader (French, English, Dutch, Spanish, Italian), clinical case or case series, prospective or retrospective study, systematic review or meta-analysis, evaluation of the therapeutic management of PRCA associated with thymoma and individual case data available. The research was supplemented by screening the references of the selected articles. There was no selection based on the year of publication.

The following variables were collected from each eligible article: age, sex, performance status, thymoma characteristics (Histologic and stage classifications,), thymoma treatment (surgery, chemotherapy, radiotherapy, multimodal) and response to treatment, time of PRCA onset (at diagnosis of the thymoma or the current therapeutic line), assessment and biological

characteristics of anemia (iron, B9, B12, parvovirus B19, Hb level, reticulocytes, EPO, myelogram…), other blood cell dysfunction (platelets, white blood cells), other paraneoplastic syndrome (myasthenia gravis, Good's syndrome ...), PRCA treatment and its response, evolution of the thymoma compared to PRCA, eventual death and its etiology. The PRCA evolution on treatment was arbitrarily classified into three categories: complete remission (CR) for return to normal hemoglobinemia, partial remission (PR) for persisting anemia not requiring transfusion as opposed to transfusion dependence of persistent disease (PD).

Descriptive statistics are limited to mean and median calculations performed with "Excel" software**.**

4. Results

Overall (figure 2), 136 articles were retained, including 119 case reports and 17 case series, published between 1950 and 2019. Three case series were excluded: a Japanese national cohort [11], a French observational study [12] and an American cohort [13] because they overlapped with selected clinical cases described more precisely in other publications. WE found one old systematic review [14]; we retained its illustrative clinical case, but the other bibliographical references cannot be retrieved.

For each clinical case, all the therapeutic lines were evaluated individually (table 2 in appendix). PRCA diagnoses were reported by identifying the time of occurrence in relation to the therapeutic line and the status of the thymic disease. Overall, there were 185 clinical cases corresponding to 312 therapeutic lines.

PRCA occurred most frequently at thymoma diagnosis (111/185). Sixty-two PRCA occurred after a median thymic disease duration of 36 months. In 12 cases, PRCA was diagnosed before thymoma discovery (Table 2 in appendix).

Figure 2: Flow chart

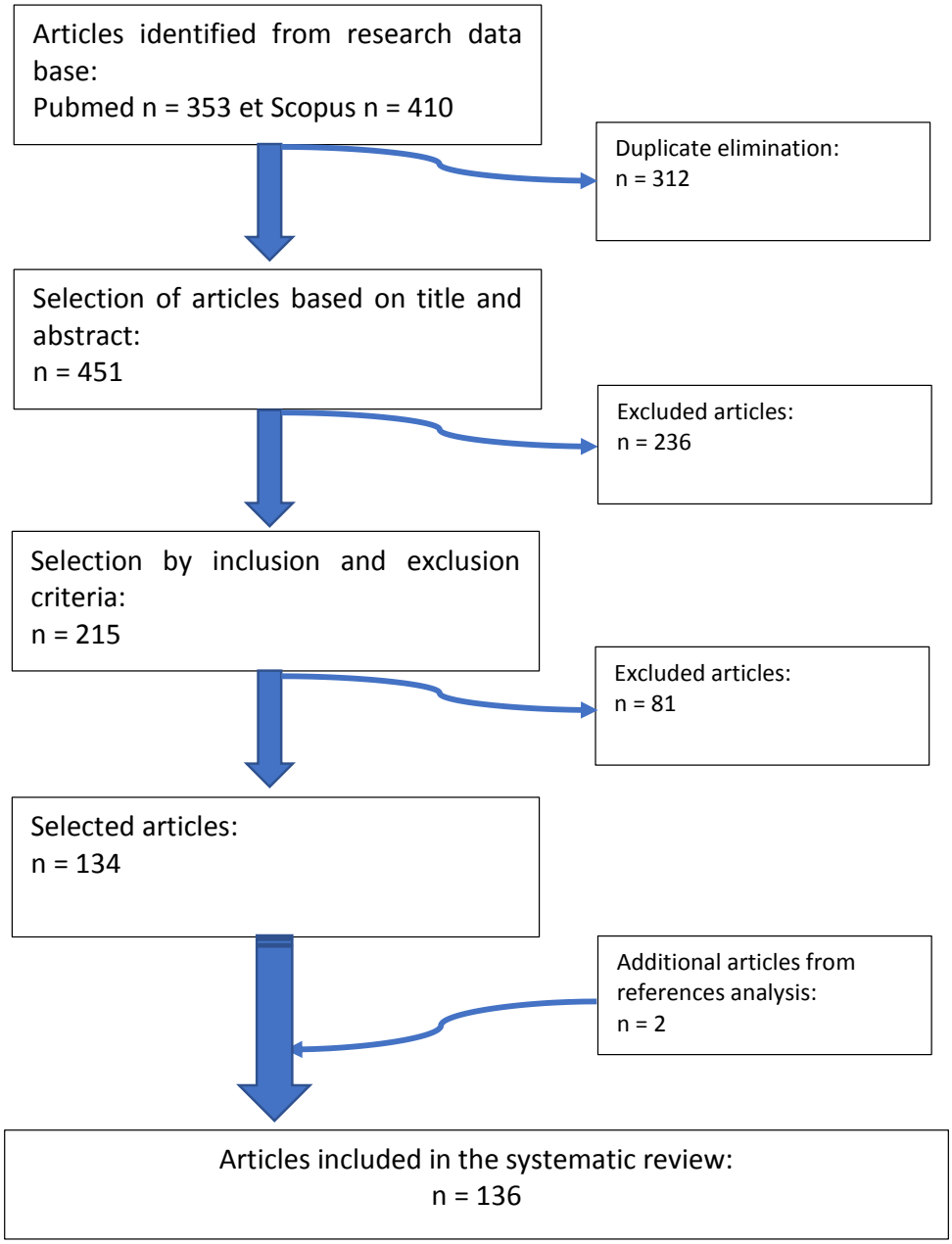


Table 3: PRCA responses in function of the treatment applied

Therapeutic sequence	CR	PR	PD
Anti-tumor treatment:			
- **Thymectomy**	**23**	**6**	**50**
- **Thymectomy + Chemotherapy**	**2**	**-**	**1**
- **Thymectomy + Radiotherapy**	**4**	**1**	**4**
- **Thymectomy + Chemotherapy + Radiotherapy**	**-**	**-**	**1**
- **Chemotherapy**	**-**	**1**	**3**
- **Radiotherapy**	**-**	**-**	**1**
- **Chemotherapy + Radiotherapy**	**-**	**-**	**1**
- **Total**	**29**	**8**	**61**
Treatments acting on the immune system:			
- **Corticosteroids**	**25**	**5**	**31**
- **Cyclosporin**	**23**	**3**	**5**
- **Cyclophosphamide**	**2**	**-**	**2**
- **Azathioprine**	**1**	**-**	**2**
- **Others IST unspecified**	**6**	**-**	**2**
- **Other monotherapy***	**8**	**5**	**14**
- **Corticoids + Cyclophosphamide**	**9**	**1**	**7**
- **Corticoids + Cyclosporin**	**3**	**-**	**4**
- **Others combinations**	**4**	**4**	**15**
- **Total**	**81**	**18**	**82**
Combination of anti-tumor treatment and treatments acting on the immune system:			
- **Thymectomy + Corticoids**	**6**	**4**	**2**
- **Thymectomy + Combination IST**	**3**	**1**	**1**
- **Thymectomy + Corticoids + Cyclosporin**	**1**	**-**	**-**
- **Chemotherapy + Combination IST**	**2**	**-**	**2**
- **Chemotherapy + Radiotherapy + Corticoids**	**-**	**-**	**1**
- **Radiotherapy + Combination IST**	**1**	**4**	**1**
- **Total**	**13**	**9**	**7**

Numbers are presenting the number of patients in each category

**adrenocorticotropic hormone; androgens; rituximab; splenectomy; anti-thymocytes globulins; immunoglobulins; bone marrow allograft; plasmapherese.*

IST, Immunosuppressive treatments

Table 3 summarizes the response of PRCA according to the applied treatment, divided into three groups (anti-tumor treatment, immune-mediated treatment, or a combination of the two approaches). Overall, tumor treatments resulted in 29.6% CR. Thymectomy alone or in combination with other therapies showed a 31.5% CR rate, whereas chemotherapy and/or radiotherapy without thymectomy showed quite none. Treatments acting on the immune system showed a CR rate of 45%, 74% with cyclosporine compared to 41% after corticosteroids. Corticosteroid-cyclophosphamide and corticosteroid-cyclosporin combinations have CR rates of 53% and 43%. Combination treatments of anti-tumor treatment and treatments acting on the immune system have a CR rate of 45%. Combinations including thymectomy had a 56% CR rate versus 27% CR for combinations without thymectomy.

Table 4: PRCA responses according to the type of thymic resections:

Type of resection:	Complete	Incomplete	No
PRCA responses:			
- **Complete remission**	**82 (58%)**	**4 (40%)**	**16 (55%)**
- **Partial Remission**	**14 (10%)**	**2 (20%)**	**4 (14%)**
- **Persistent disease**	**45 (32%)**	**4 (40%)**	**9 (31%)**
- **Total**	**141**	**10**	**29**

This table shows the response of PRCA depending on the type of thymic resections. Complete thymic resections appear to have better CR rate than incomplete resections.

When PRCA persisted after thymectomy remission was essentially achieved with immunomodulatory treatments. Overall PRCA complete remission rate in these cases PRCA persistence post-thymectomy are approximately 50% regardless of the treatment line applied (Table 5).

Complete remission of PRCA was associated in 70% of cases with thymic CR while persistent PRCA (PD) does not appear to be associated with progressing thymoma (Table 6).

Table 5: PRCA rescue therapy and responses in case of PRCA persistence post-thymectomy

2nd line (N=44)*		3rd line (N=17)		More than 3 lines (N=11)	
Chemotherapy	1 PD	Allograft	1 CR 1 PR	Corticoids	2 CR 1 PD
Corticosteroids	7 CR 8 PD	Corticosteroids	2 CR 1 PD	Cyclosporine	2 CR 1PD
Cyclosporin	3 CR 2 PR	Cyclosporin	3 CR	Immunoglobulins	1 PR
CPA	2 PD	Immunoglobulins	1 PD	Others IST	1 CR
Azathioprine	1 CR	ATG	1 PD	Combinations	2 PD
Androgens	1 CR 2 PD	Androgens	1 PD	ACTH	1 CR
Others IST	3 CR	Splenectomy	1 CR 1PD		
Combinations	6 CR 1PR 7PD	Combinations	2 CR 2PD		

Abbreviations: CPA, Cyclophosphamide; ATG, antithymocyte globulins; IST, Immunosuppressive treatments, ACTH ; Adrenocorticotropic hormone.

PRCA response according to Masaoka stage could be assessed in 46 cases; there were 15 CR out of 29 stage I or II and 9 CR out of 17 stage III and IV thymoma (p = 0.94). Also, we did not observe any influence of histology with 10 CR out of 26 cases for types A, AB and B1 and 7 CR out of 11 cases in types B2 and B3 (p = 0.15).

The median duration of PRCA CR was 18 months after immunomodulatory treatment versus 15 months after anti-tumor treatment alone or in combination with an IST treatment. There was no effect of PRCA onset and CR, with 60% versus 55% CR when PRCA occurred at thymoma diagnosis or during the course of the disease. Five cases of spontaneous remission were observed and an average of 1.7 PRCA flare-ups (persistence/worsening despite treatment) were identified per patient.

Twenty-one relapses of PRCA were identified including only five in parallel to the thymic relapse. There were 58 reported deaths. Eight are directly attributable to thymic progression. The majority (n=36) are secondary to PRCA treatment with infectious origin (n=25 including 20 on immunomodulatory therapy) and 6 in the context of systemic hemosiderosis.

Table 6 PRCA's response according to the status of the thymoma

PRCA's response	Progressive status of thymoma
Complete remission : **106**	Complete remission : **74** Partial remission : 5 Stable Disease: 5 Progressive Disease: 13 No information : 9
Partial remission: **23**	Complete remission : 14 Partial remission: **1** Stable disease : 1 Progressive disease: 4 No information : 3
Persistent disease: **51**	Complete remission : 23 Partial remission: 4 Stable disease: 4 Progressive disease: **15** No information : 5

5. Discussion

We present an illustrative clinical case of PRCA diagnosed during the course of stage IVA thymoma, with parallel PRCA and thymoma partial remission during chemotherapy. A systematic review was conducted in order assessing the best therapeutic option for controlling this rare paraneoplastic syndrome.

Thymectomy is the therapeutic cornerstone for thymoma, whatever alone or in a multimodal approach. It is also the main antitumoral and the most effective therapeutic option for PRCA, essentially for the first line care of PRCA. Only six documented cases were treated only with chemotherapy and/or radiotherapy with only one reported PR. Our clinical case corresponds to a very rare situation of PRCA partial response with chemotherapy alone. The results from the systematic review are supporting the role of thymectomy as a key factor for

controlling PRCA [15, 16]. The combination of thymectomy with radiotherapy shows good results (44% of CR, table 3) but this must again be qualified by the low number of cases studied

The better CR rate with a complete thymic resection (Table 4) is only exploratory value as the number of incomplete resections is small. The same observation can be made regarding the comparison between complete thymectomy versus no thymectomy.

Due to the scarcity of the disease, there is no controlled trial comparing therapeutic attitude "with" versus "without" thymectomy. In the present setting, data with thymectomy may be biased by selection of less aggressive thymomas, particularly stages I and II and type A or AB. However, we did not find a difference in the control rate of PRCA depending on Masaoka stage or histological subtypes (A, AB, B1 versus B2 and B3). Our data report a predominance of type B1 thymomas associated with PRCAs represented at 31% against 13% usually in the general population [17]. The value of those analyses is limited by the low number of published cases and the changes in classifications over time [18].

Treatments with immunomodulatory action, mainly cyclosporin and corticosteroids demonstrated in this systematic review their interest in the management of PRCA, whatever in first-line or in case or PRCA recurrence. Japanese [11] and American [13] national cohorts reported similar figures. These results are in contradiction with a French observational study [12] in which corticosteroid were most effective. Finally, combination therapies (anti-tumor + IST) do not show a better efficacy in terms of CR rate than immunomodulatory treatments but do expose to an increased risk of side effects, whereas an anti-tumor treatment alone may be sufficient in one third of cases.

The PRCA onset is generally at thymoma diagnosis while one-third occurred later. Most of the clinical cases (158/185) were confirmed by a bone marrow aspiration. As for all

retrospective analyses, and particularly here as the data records are done on a very large time period, it is not possible going back to the initial data. So, we may only consider the diagnosis provided by the authors of the case reports. Our case occurred concomitantly with a thymic relapse. Other differential diagnoses were reasonably excluded. PRCA secondary to anti-EPO antibodies is not consistent with high EPO level and PR under chemotherapy [19]. Thymoma bone marrow infiltration or post-anthracycline leukemia were excluded by multiple bone marrow aspiration and biopsy. Infections as parvovirus B19 were negative and the discrete chronic gastritis did not explain such anemia. It is also questionable whether the anemia (6 months prior to PRCA) attributed to the first cycle of chemotherapy is not already representative for the start of PRCA but this anemia responded to EPO and did not recur when chemotherapy was stopped.

The terminal course is marked by the development of bicytopenia (neutropenia-anemia), for which the diagnosis of MAS was suggested due to the presence of both biological (bicytopenia, hypertriglyceridemia, hyperferritinemia, CD25 increased) and clinical (pyrexia and skin lesions) criteria. The H-Score is 169 corresponding to a probability of 78% [10]. The etiology of MAS could be active thymoma or infection. No hemagophagocytosis was seen at bone marrow aspirate and myelogram ruled out leukemia or medullar invasion. Nevertheless, the low cellularity should suggest a relapse of PRCA coupled with paraneoplastic neutropenia. Approximately 10 cases of white blood cell aplasia secondary to thymoma have been described and could be treated by thymectomy or immunosuppression [20]. There were also five cases in the French cohort [12]. No association of PRCA and agranulocytosis was found in the literature. In our systematic review, there were only two cases of leukopenia associated with PRCA, but they did not show neutropenia. However, the association PRCA with amegacaryocyte thrombocytopenia was described and there are more than ten cases in our systematic review. Finally, two cases of pancytopenia were reported but without neutropenia. A systematic review

of the few cases of pancytopenia associated with thymomas was suggesting a therapeutic role for immunosuppressive drugs [21].

In our systematic review, we observed that complications secondary to PRCA treatment are representing the largest cause of death, particularly by infection secondary to immunosuppression. Other authors found the same findings with cyclosporin and recommended careful monitoring of patients undergoing IST treatment [11]. The French review even suggests the use of rituximab to avoid immunosuppression based on their two cases of CR out of 4 treated [12]. However, there was only one case treated with rituximab in our review showing PR.

This systematic review has some limitations. The data reported in the selected clinical cases are very heterogeneous, particularly with regard to thymic characteristics (stage and type, duration and type of treatment, type of response), PRCA (diagnostic means, duration and type of treatment, duration and type of response) and patient follow-up (duration of follow-up, possible cause of death). Criteria for PRCA remission are based on the normal hemoglobin level and independence from transfusion but do not take into account the duration or decrease in frequency of transfusion. We defined arbitrarily these criteria in the absence of literature consensus. Corticosteroid was considered by default as treatment for PRCA except when explicitly described as an anti-tumor therapy. We did not select foreign language articles that were inaccessible to readers: sixty articles in Japanese, four in German, two in Korean, two in Chinese, one in Danish and one in Russian were excluded while some Japanese articles translated into English from other journals were retained. Finally, the analysis by therapeutic line does not reveal the influence of previous therapies on the final PRCA control.

6. Conclusion:

In this systematic review, thymectomy appears to be the most effective anti-tumor therapy for PRCA associated thymoma. Other anti-tumor treatments may induce partial remissions, but no case of complete remission was reported. If PRCA persists after thymectomy, immunomodulatory therapy should be considered with cyclosporin having the best CR, taking into account the risk of infectious complications. The respective place of anti-tumor and immunomodulatory treatments for PRCA, or their combination must be validated in prospective clinical studies.

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Title: Management of thymoma associated autoimmune pure red cell aplasia: case report and systematic review of the literature.

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Highlights:

- Thymectomy is the most effective therapy for thymoma associated PRCA
- If PRCA persists after thymectomy, immunomodulatory therapy particularly cyclosporine, is effective.

Abstract

Pure red cell aplasia (PRCA) is a rare paraneoplastic syndrome observed in 2-5% of thymomas. Literature reports great variability in its management. Based on an illustrative clinical case, we present a systematic literature review whose main objective is to evaluate the therapeutic management of PRCA. The literature search was performed based on the PICO method in the Medline and Scopus databases. The reference clinical case concerns a 51-year-old woman with stage IVa thymoma. After initial response to chemotherapy, a locoregional progression occurred with PRCA development that responded favorably under second line chemotherapy. The patient finally died in a context of bicytopenia with febrile neutropenia. The systematic review covers 132 articles published between 1950 and 2019. Thymectomy alone or in combination with other therapies showed a 31% complete remission (CR) rate for PRCA of, whereas none was reported with anti-tumor treatments without thymectomy. Among immunomodulatory therapies, cyclosporin gave the highest percentage of CR (74%). Finally, the combination of thymectomy and immunomodulatory treatments showed a CR rate of 45%. Thymectomy appeared to be the most effective anti-tumor treatment for PRCA. Immunomodulatory therapies, particularly cyclosporine, are shown effective, but the risk of infectious complications must be considered. The optimal place of anti-tumor and immunomodulatory therapies against PRCA has yet to be determined.

Keywords: Pure red cell aplasia, erythroblastopenia, thymoma, thymic carcinoma, systematic review, clinical case.

1. Introduction

Thymoma associated pure red cell aplasia (PRCA) is a rare disorder linked to thymoma that could be an autoimmune phenomenon, as myasthenia [1, 2]. Some etiologies are proposed: role of self-reactive T-cells, clonal lymphocyte disorder and anti-erythroblast antibodies [3-5]. Classical symptoms of anemia such as fatigue, weakness, pallor or dyspnea may reveal PRCA. PRCA may be found at time of thymoma diagnosis or may develop several years later [6]. It is usually a non-regenerative, normocytic, or sometimes macrocytic anemia. Bone marrow examination generally shows a normal abundance of myeloid cells and megakaryocytes contrasting with the complete absence of erythroblasts [5, 7]. Published data are essentially case reports with a great variability concerning the time of onset of aplasia, its evolution and management [7, 8]. Therapeutic options consist of supportive treatments (iterative transfusions, erythropoietin [EPO]), Immunosuppressive/immunomodulatory treatments (corticosteroid therapy, cyclosporin...) or oncological treatments (thymectomy, radiotherapy, chemotherapy) [8, 9].

Based on an illustrative clinical case, we conducted a systematic review of the literature on the management of thymoma-associated PRCA. Its main objective is to evaluate the impact of thymoma treatment on the therapeutic management of PRCA. The Jules Bordet Institute's ethics committee approved the research protocol on 6/12/2018. (Reference CE 2921).

2. Clinical Case:

A 51-year-old woman was referred for management of a stage IVa B1 thymoma, discovered incidentally on a chest X-ray. Her past medical history is limited to an operated leiomyosarcoma two years before. She neither smoked nor drank and was taking only vitamin D and hormone replacement therapy for menopause.

Initial lab tests were normal including a complete blood count. The tumor was initially unresectable (extensive pleural involvement). Chemotherapy combining cisplatin, adriamycin, cyclophosphamide was started. After the third cycle, the patient presented a mild regenerative anemia with hemoglobin (Hb) level at 10.2 g/dl which was attributed to chemotherapy. She received a subcutaneous injection of EPO (epoetin alpha 40000UI/week). After the fourth cycle of chemotherapy, a morphological and metabolic response of the thymoma was demonstrated. Pleuro-pneumectomy was denied by the patient. She was later hospitalized for a cerebral hemorrhage secondary to central venous thrombosis, four weeks after the first EPO injection. The chemotherapy and EPO were stopped.

Six months later, the disease slowly progressed essentially at the pleural level. There was no anemia and no clinical impact for 9 months. The patient refused to resume chemotherapy. Nineteen months after diagnosis, she was admitted for dyspnea (grade 3 according to modified Medical Research Council dyspnea scale) associated with tinnitus and palpitations. The biology showed normocytic anemia at 6.2 g/dl with reticulocytopenia. There was no iron, vitamin B9 or B12 deficiency (Table 1)**.** Serologies for parvovirus B19 were negative. The EPO level was high. The fecal occult blood tests were negative, and a gastroscopy revealed mild chronic gastritis. Subsequently, a bone marrow biopsy showed aplasia of the erythroid lineage without excess blasts, while the myeloid and megakaryocyte lineages remained within norms. The OGATA score was 0, excluding myelodysplasia. Lymphocyte B were absent and the CD4/CD8 ratio was reduced. After collegial discussion with the hematologists, the diagnosis of PRCA secondary to the thymoma was retained [7]; a possible responsibility of erythropoietin administration was considered unlikely. The patient was transfused with red blood cells several times in view of the symptoms (Figure 1).

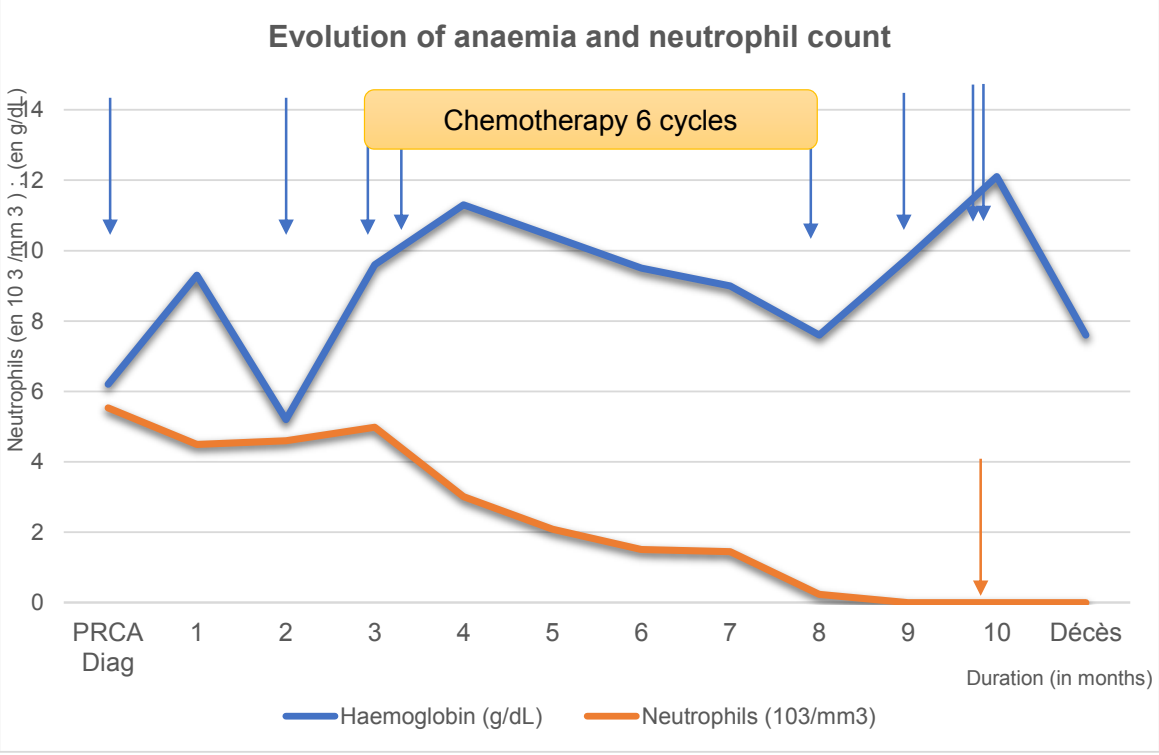
Three months later, the patient agreed to resume cisplatin-adriamycin-cyclophosphamide. In parallel with tumor regression, the patient became transfusion-

Table 1: General laboratory analyses

Laboratory	At Diagnostic of PRCA	At bicytopenia	Reference values
Hemoglobin	6.2	9.8	12-16 g/dl
MCV	94	94	80-100 fL
Reticulocytes	$4x10^3$	$45.8x10^3$	$22.5\text{-}147x10^3/\mu L$
Haptoglobin	162	/	30-200 mg/dL
Ferritin	519	2060	30-350 µg/L
Serum iron	182	18	50-170 µg/dL
Transferrin	225	116	250-380 mg/dL
Tf saturation	58	11	15-50%
Vitamin B9	7.5	12.5	> 4.6 µg/L
Vitamin B12	388	659	197-771 ng/L
CRP	38	175.6	< 10mg/L
Erythropoietin	2453	/	1-9 U/L
Leukocytes	12280	1790	3500-11000/µL
Neutrophils	$5.53x10^3$	0	1.5-6.7x10/µL
Monocytes	$0.25x10^3$	$0.07x10^3$	$0.2\text{-}1x10^3/\mu L$
Basophiles	0	0	$<0.1x10^3/\mu L$
Eosinophils	0	0	$<0.4x10^3/\mu L$
Lymphocytes	$6.51x10^3$	$1.72x10^3$	$1.2\text{-}3.5x10^3/\mu L$
Platelets	$345x10^3$	$301x10^3$	$150\text{-}440x10^3$/microL

Abbreviations: CRP, C reactive protein; MCV, mean corpuscular volume; Tf , transferrin.

Figure 1: Clinical case graph on the evolution of anemia and neutrophil count over time



Blue arrow = transfusion concentrated red blood cells; Orange arrow = filgrastim injection.

Abbreviations: Diag, diagnosis; Hb, hemoglobin; PMN, neutrophils.

independent for 5 months and partially controlled anemia between 9 and 11 g/dl during chemotherapy cycles 2 to 5. After the latter cycle, the patient had to be transfused again due to recurrence of anemia symptoms. At that time, it was difficult to distinguish whether this recurrence is secondary to the chemotherapy or to the PRCA relapse.

At the end of the 6th course of chemotherapy (Adriamycin cumulative dose 316 mg/m²), the patient was hospitalized for febrile neutropenia. There was no tumor recurrence at chest scanner. The blood count showed a persistence of anemia at 9.8 g/dl and a complete absence of neutrophils. A new bone marrow aspiration showed a hypocellular bone marrow containing only a few megakaryocytes. There were no abnormal cells, no plasmocytes and a normal CD4/CD8 ratio without B lymphocytes. A bone marrow biopsy showed no evidence of leukemia, thymoma invasion or macrophage activation syndrome (MAS). Under antibiotic therapy, the patient improved progressively. She received red blood cells transfusions, and 6 injections of filgrastim with no effect on neutropenia. Three weeks later, the patient presented a new episode of febrile neutropenia with positive blood cultures for *Serratia marcescens*. Clinically, the patient presents a vesicular rash suspicious of zona and we start Aciclovir. The patient never presented mucosal lesions, making a Steven Johnson syndrome unlikely. Despite a quick improvement of skin lesions and broad-spectrum antibiotic, the patient deteriorate continuously. A new marrow aspiration showed low cellularity with almost exclusive presence of T-lymphocytes (97%) without phenotypic abnormalities. A macrophagic activation syndrome was suspected in the face of an elevation of the CD25a marker, hyperferritinemia, hypertriglyceridemia, bicytopenia and pyrexia [10] but no hemagophagocytosis was seen at bone marrow aspirate. This bicytopenia could also correspond to a paraneoplastic syndrome as a progression of the thymoma was seen. The patient denied additional investigations and treatment with etoposide-dexamethasone. Palliatives cares were provided. The patient died in a context of multi-organ failure with persistent bicytopenia, blood transfusions dependency and

candidemia (*C. tropicalis*), despite caspofungin and broad-spectrum antibiotics. The family refused an autopsy.

3. Materials and methods

We performed a systematic review of the literature on autoimmune PRCA associated with thymoma. The literature search was conducted using the PICO (Population, Intervention, Comparator, Outcome) technique for the formulation of the research equation: P = Patients with PRCA secondary to a thymoma; I = anti-tumor treatment (systemic, radiotherapy, surgery); C = iterative transfusions of red blood cells; O = resolution of anemia.

The corresponding research criteria of "P" were translated into MeSH terms, and free-text keywords that were searched for in title and abstracts. An experienced medical scientific librarian performed literature search in December 2019 using the Medline database via the OvidSP interface. This research equation was adapted for use in the Scopus database. A first selection based on the title and the abstract content was made by independent double reading by two authors (BL and TB). Articles selected by at least one of the two readers were retained for full reading.

Selections criteria were: language accessible to the reader (French, English, Dutch, Spanish, Italian), clinical case or case series, prospective or retrospective study, systematic review or meta-analysis, evaluation of the therapeutic management of PRCA associated with thymoma and individual case data available. The research was supplemented by screening the references of the selected articles. There was no selection based on the year of publication.

The following variables were collected from each eligible article: age, sex, performance status, thymoma characteristics (Histologic and stage classifications,), thymoma treatment (surgery, chemotherapy, radiotherapy, multimodal) and response to treatment, time of PRCA onset (at diagnosis of the thymoma or the current therapeutic line), assessment and biological

characteristics of anemia (iron, B9, B12, parvovirus B19, Hb level, reticulocytes, EPO, myelogram…), other blood cell dysfunction (platelets, white blood cells), other paraneoplastic syndrome (myasthenia gravis, Good's syndrome ...), PRCA treatment and its response, evolution of the thymoma compared to PRCA, eventual death and its etiology. The PRCA evolution on treatment was arbitrarily classified into three categories: complete remission (CR) for return to normal hemoglobinemia, partial remission (PR) for persisting anemia not requiring transfusion as opposed to transfusion dependence of persistent disease (PD).

Descriptive statistics are limited to mean and median calculations performed with "Excel" software**.**

4. Results

Overall (figure 2), 136 articles were retained, including 119 case reports and 17 case series, published between 1950 and 2019. Three case series were excluded: a Japanese national cohort [11], a French observational study [12] and an American cohort [13] because they overlapped with selected clinical cases described more precisely in other publications. WE found one old systematic review [14]; we retained its illustrative clinical case, but the other bibliographical references cannot be retrieved.

For each clinical case, all the therapeutic lines were evaluated individually (table 2 in appendix). PRCA diagnoses were reported by identifying the time of occurrence in relation to the therapeutic line and the status of the thymic disease. Overall, there were 185 clinical cases corresponding to 312 therapeutic lines.

PRCA occurred most frequently at thymoma diagnosis (111/185). Sixty-two PRCA occurred after a median thymic disease duration of 36 months. In 12 cases, PRCA was diagnosed before thymoma discovery (Table 2 in appendix).

Figure 2: Flow chart

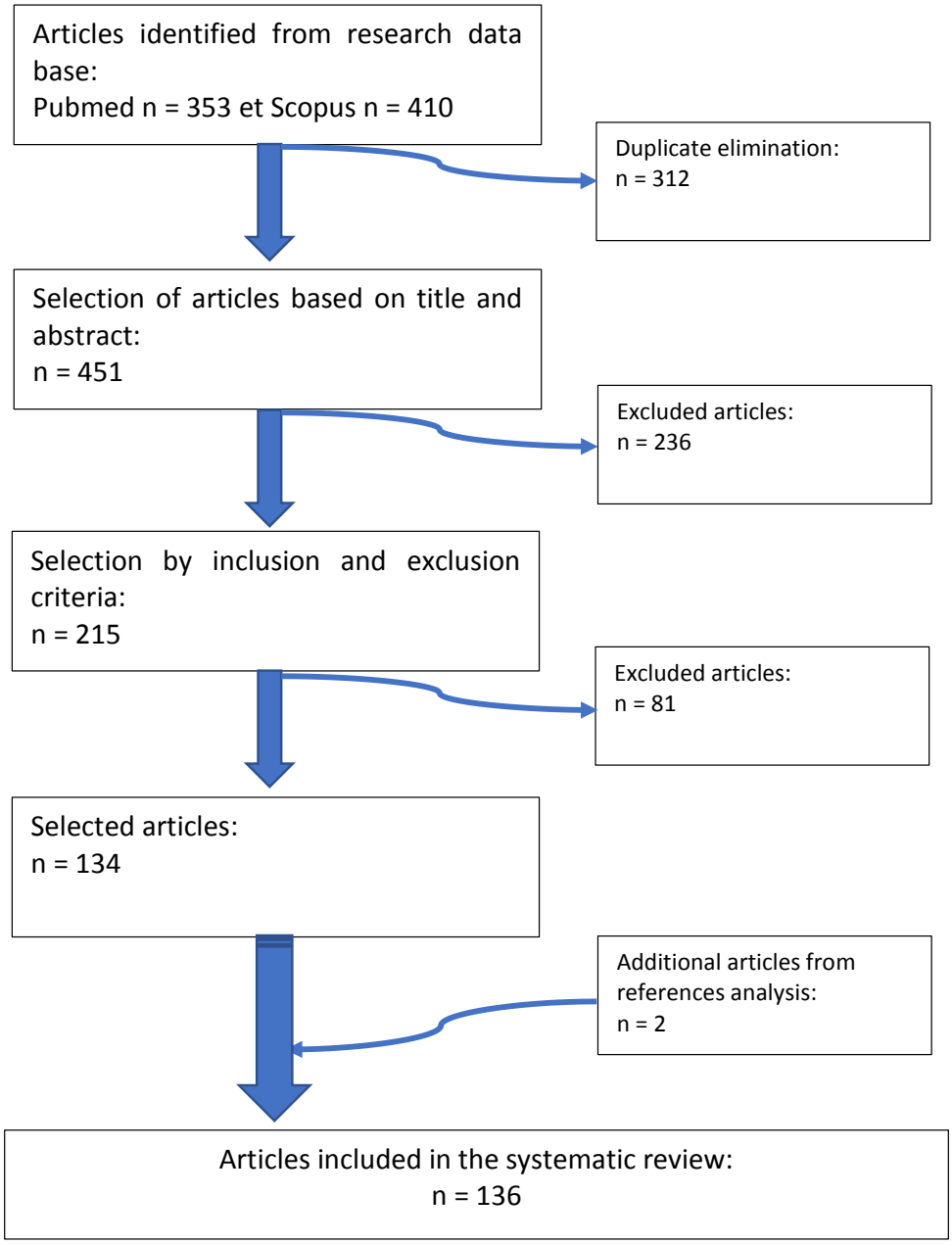


Table 3: PRCA responses in function of the treatment applied

Therapeutic sequence	CR	PR	PD
Anti-tumor treatment:			
- **Thymectomy**	**23**	**6**	**50**
- **Thymectomy + Chemotherapy**	**2**	**-**	**1**
- **Thymectomy + Radiotherapy**	**4**	**1**	**4**
- **Thymectomy + Chemotherapy + Radiotherapy**	**-**	**-**	**1**
- **Chemotherapy**	**-**	**1**	**3**
- **Radiotherapy**	**-**	**-**	**1**
- **Chemotherapy + Radiotherapy**	**-**	**-**	**1**
- **Total**	**29**	**8**	**61**
Treatments acting on the immune system:			
- **Corticosteroids**	**25**	**5**	**31**
- **Cyclosporin**	**23**	**3**	**5**
- **Cyclophosphamide**	**2**	**-**	**2**
- **Azathioprine**	**1**	**-**	**2**
- **Others IST unspecified**	**6**	**-**	**2**
- **Other monotherapy***	**8**	**5**	**14**
- **Corticoids + Cyclophosphamide**	**9**	**1**	**7**
- **Corticoids + Cyclosporin**	**3**	**-**	**4**
- **Others combinations**	**4**	**4**	**15**
- **Total**	**81**	**18**	**82**
Combination of anti-tumor treatment and treatments acting on the immune system:			
- **Thymectomy + Corticoids**	**6**	**4**	**2**
- **Thymectomy + Combination IST**	**3**	**1**	**1**
- **Thymectomy + Corticoids + Cyclosporin**	**1**	**-**	**-**
- **Chemotherapy + Combination IST**	**2**	**-**	**2**
- **Chemotherapy + Radiotherapy + Corticoids**	**-**	**-**	**1**
- **Radiotherapy + Combination IST**	**1**	**4**	**1**
- **Total**	**13**	**9**	**7**

Numbers are presenting the number of patients in each category

**adrenocorticotropic hormone; androgens; rituximab; splenectomy; anti-thymocytes globulins; immunoglobulins; bone marrow allograft; plasmapherese.*

IST, Immunosuppressive treatments

Table 3 summarizes the response of PRCA according to the applied treatment, divided into three groups (anti-tumor treatment, immune-mediated treatment, or a combination of the two approaches). Overall, tumor treatments resulted in 29.6% CR. Thymectomy alone or in combination with other therapies showed a 31.5% CR rate, whereas chemotherapy and/or radiotherapy without thymectomy showed quite none. Treatments acting on the immune system showed a CR rate of 45%, 74% with cyclosporine compared to 41% after corticosteroids. Corticosteroid-cyclophosphamide and corticosteroid-cyclosporin combinations have CR rates of 53% and 43%. Combination treatments of anti-tumor treatment and treatments acting on the immune system have a CR rate of 45%. Combinations including thymectomy had a 56% CR rate versus 27% CR for combinations without thymectomy.

Table 4: PRCA responses according to the type of thymic resections:

Type of resection:	Complete	Incomplete	No
PRCA responses:			
- **Complete remission**	**82 (58%)**	**4 (40%)**	**16 (55%)**
- **Partial Remission**	**14 (10%)**	**2 (20%)**	**4 (14%)**
- **Persistent disease**	**45 (32%)**	**4 (40%)**	**9 (31%)**
- **Total**	**141**	**10**	**29**

This table shows the response of PRCA depending on the type of thymic resections. Complete thymic resections appear to have better CR rate than incomplete resections.

When PRCA persisted after thymectomy remission was essentially achieved with immunomodulatory treatments. Overall PRCA complete remission rate in these cases PRCA persistence post-thymectomy are approximately 50% regardless of the treatment line applied (Table 5).

Complete remission

of PRCA was associated in 70% of cases with thymic CR while persistent PRCA (PD) does not appear to be associated with progressing thymoma (Table 6).

Table 5: PRCA rescue therapy and responses in case of PRCA persistence post-thymectomy

2nd line (N=44)*		3rd line (N=17)		More than 3 lines (N=11)	
Chemotherapy	1 PD	Allograft	1 CR 1 PR	Corticoids	2 CR 1 PD
Corticosteroids	7 CR 8 PD	Corticosteroids	2 CR 1 PD	Cyclosporine	2 CR 1PD
Cyclosporin	3 CR 2 PR	Cyclosporin	3 CR	Immunoglobulins	1 PR
CPA	2 PD	Immunoglobulins	1 PD	Others IST	1 CR
Azathioprine	1 CR	ATG	1 PD	Combinations	2 PD
Androgens	1 CR 2 PD	Androgens	1 PD	ACTH	1 CR
Others IST	3 CR	Splenectomy	1 CR 1PD		
Combinations	6 CR 1PR 7PD	Combinations	2 CR 2PD		

Abbreviations: CPA, Cyclophosphamide; ATG, antithymocyte globulins; IST, Immunosuppressive treatments, ACTH ; Adrenocorticotropic hormone.

PRCA response according to Masaoka stage could be assessed in 46 cases; there were 15 CR out of 29 stage I or II and 9 CR out of 17 stage III and IV thymoma ($p = 0.94$). Also, we did not observe any influence of histology with 10 CR out of 26 cases for types A, AB and B1 and 7 CR out of 11 cases in types B2 and B3 ($p = 0.15$).

The median duration of PRCA CR was 18 months after immunomodulatory treatment versus 15 months after anti-tumor treatment alone or in combination with an IST treatment. There was no effect of PRCA onset and CR, with 60% versus 55% CR when PRCA occurred at thymoma diagnosis or during the course of the disease. Five cases of spontaneous remission were observed and an average of 1.7 PRCA flare-ups (persistence/worsening despite treatment) were identified per patient.

Twenty-one relapses of PRCA were identified including only five in parallel to the thymic relapse. There were 58 reported deaths. Eight are directly attributable to thymic progression. The majority (n=36) are secondary to PRCA treatment with infectious origin

(n=25 including 20 on immunomodulatory therapy) and 6 in the context of systemic hemosiderosis.

Table 6 PRCA's response according to the status of the thymoma

PRCA's response	Progressive status of thymoma
Complete remission : **106**	Complete remission : **74** Partial remission : 5 Stable Disease: 5 Progressive Disease: 13 No information : 9
Partial remission: **23**	Complete remission : 14 Partial remission: **1** Stable disease : 1 Progressive disease: 4 No information : 3
Persistent disease: **51**	Complete remission : 23 Partial remission: 4 Stable disease: 4 Progressive disease: **15** No information : 5

5. Discussion

We present an illustrative clinical case of PRCA diagnosed during the course of stage IVA thymoma, with parallel PRCA and thymoma partial remission during chemotherapy. A systematic review was conducted in order assessing the best therapeutic option for controlling this rare paraneoplastic syndrome.

Thymectomy is the therapeutic cornerstone for thymoma, whatever alone or in a multimodal approach. It is also the main antitumoral and the most effective therapeutic option for PRCA, essentially for the first line care of PRCA. Only six documented cases were treated

only with chemotherapy and/or radiotherapy with only one reported PR. Our clinical case corresponds to a very rare situation of PRCA partial response with chemotherapy alone. The results from the systematic review are supporting the role of thymectomy as a key factor for controlling PRCA [15, 16]. The combination of thymectomy with radiotherapy shows good results (44% of CR, table 3) but this must again be qualified by the low number of cases studied

The better CR rate with a complete thymic resection (Table 4) is only exploratory value as the number of incomplete resections is small. The same observation can be made regarding the comparison between complete thymectomy versus no thymectomy.

Due to the scarcity of the disease, there is no controlled trial comparing therapeutic attitude "with" versus "without" thymectomy. In the present setting, data with thymectomy may be biased by selection of less aggressive thymomas, particularly stages I and II and type A or AB. However, we did not find a difference in the control rate of PRCA depending on Masaoka stage or histological subtypes (A, AB, B1 versus B2 and B3). Our data report a predominance of type B1 thymomas associated with PRCAs represented at 31% against 13% usually in the general population [17]. The value of those analyses is limited by the low number of published cases and the changes in classifications over time [18].

Treatments with immunomodulatory action, mainly cyclosporin and corticosteroids demonstrated in this systematic review their interest in the management of PRCA, whatever in first-line or in case or PRCA recurrence. Japanese [11] and American [13] national cohorts reported similar figures. These results are in contradiction with a French observational study [12] in which corticosteroid were most effective. Finally, combination therapies (anti-tumor + IST) do not show a better efficacy in terms of CR rate than immunomodulatory treatments but

do expose to an increased risk of side effects, whereas an anti-tumor treatment alone may be sufficient in one third of cases.

The PRCA onset is generally at thymoma diagnosis while one-third occurred later. Most of the clinical cases (158/185) were confirmed by a bone marrow aspiration. As for all retrospective analyses, and particularly here as the data records are done on a very large time period, it is not possible going back to the initial data. So, we may only consider the diagnosis provided by the authors of the case reports. Our case occurred concomitantly with a thymic relapse. Other differential diagnoses were reasonably excluded. PRCA secondary to anti-EPO antibodies is not consistent with high EPO level and PR under chemotherapy [19]. Thymoma bone marrow infiltration or post-anthracycline leukemia were excluded by multiple bone marrow aspiration and biopsy. Infections as parvovirus B19 were negative and the discrete chronic gastritis did not explain such anemia. It is also questionable whether the anemia (6 months prior to PRCA) attributed to the first cycle of chemotherapy is not already representative for the start of PRCA but this anemia responded to EPO and did not recur when chemotherapy was stopped.

The terminal course is marked by the development of bicytopenia (neutropenia-anemia), for which the diagnosis of MAS was suggested due to the presence of both biological (bicytopenia, hypertriglyceridemia, hyperferritinemia, CD25 increased) and clinical (pyrexia and skin lesions) criteria. The H-Score is 169 corresponding to a probability of 78% [10]. The etiology of MAS could be active thymoma or infection. No hemagophagocytosis was seen at bone marrow aspirate and myelogram ruled out leukemia or medullar invasion. Nevertheless, the low cellularity should suggest a relapse of PRCA coupled with paraneoplastic neutropenia. Approximately 10 cases of white blood cell aplasia secondary to thymoma have been described and could be treated by thymectomy or immunosuppression [20]. There were also five cases in the French cohort [12]. No association of PRCA and agranulocytosis was found in the literature.

In our systematic review, there were only two cases of leukopenia associated with PRCA, but they did not show neutropenia. However, the association PRCA with amegacaryocyte thrombocytopenia was described and there are more than ten cases in our systematic review. Finally, two cases of pancytopenia were reported but without neutropenia. A systematic review of the few cases of pancytopenia associated with thymomas was suggesting a therapeutic role for immunosuppressive drugs [21].

In our systematic review, we observed that complications secondary to PRCA treatment are representing the largest cause of death, particularly by infection secondary to immunosuppression. Other authors found the same findings with cyclosporin and recommended careful monitoring of patients undergoing IST treatment [11]. The French review even suggests the use of rituximab to avoid immunosuppression based on their two cases of CR out of 4 treated [12]. However, there was only one case treated with rituximab in our review showing PR.

This systematic review has some limitations. The data reported in the selected clinical cases are very heterogeneous, particularly with regard to thymic characteristics (stage and type, duration and type of treatment, type of response), PRCA (diagnostic means, duration and type of treatment, duration and type of response) and patient follow-up (duration of follow-up, possible cause of death). Criteria for PRCA remission are based on the normal hemoglobin level and independence from transfusion but do not take into account the duration or decrease in frequency of transfusion. We defined arbitrarily these criteria in the absence of literature consensus. Corticosteroid was considered by default as treatment for PRCA except when explicitly described as an anti-tumor therapy. We did not select foreign language articles that were inaccessible to readers: sixty articles in Japanese, four in German, two in Korean, two in Chinese, one in Danish and one in Russian were excluded while some Japanese articles

translated into English from other journals were retained. Finally, the analysis by therapeutic line does not reveal the influence of previous therapies on the final PRCA control.

6. Conclusion:

In this systematic review, thymectomy appears to be the most effective anti-tumor therapy for PRCA associated thymoma. Other anti-tumor treatments may induce partial remissions, but no case of complete remission was reported. If PRCA persists after thymectomy, immunomodulatory therapy should be considered with cyclosporin having the best CR, taking into account the risk of infectious complications. The respective place of anti-tumor and immunomodulatory treatments for PRCA, or their combination must be validated in prospective clinical studies.

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Title: Management of thymoma associated autoimmune pure red cell aplasia: case report and systematic review of the literature.

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Highlights:

- Thymectomy is the most effective therapy for thymoma associated PRCA
- If PRCA persists after thymectomy, immunomodulatory therapy particularly cyclosporine, is effective.

Abstract

Pure red cell aplasia (PRCA) is a rare paraneoplastic syndrome observed in 2-5% of thymomas. Literature reports great variability in its management. Based on an illustrative clinical case, we present a systematic literature review whose main objective is to evaluate the therapeutic management of PRCA. The literature search was performed based on the PICO method in the Medline and Scopus databases. The reference clinical case concerns a 51-year-old woman with stage IVa thymoma. After initial response to chemotherapy, a locoregional progression occurred with PRCA development that responded favorably under second line chemotherapy. The patient finally died in a context of bicytopenia with febrile neutropenia. The systematic review covers 132 articles published between 1950 and 2019. Thymectomy alone or in combination with other therapies showed a 31% complete remission (CR) rate for PRCA of, whereas none was reported with anti-tumor treatments without thymectomy. Among immunomodulatory therapies, cyclosporin gave the highest percentage of CR (74%). Finally, the combination of thymectomy and immunomodulatory treatments showed a CR rate of 45%. Thymectomy appeared to be the most effective anti-tumor treatment for PRCA. Immunomodulatory therapies, particularly cyclosporine, are shown effective, but the risk of infectious complications must be considered. The optimal place of anti-tumor and immunomodulatory therapies against PRCA has yet to be determined.

Keywords: Pure red cell aplasia, erythroblastopenia, thymoma, thymic carcinoma, systematic review, clinical case.

1. Introduction

Thymoma associated pure red cell aplasia (PRCA) is a rare disorder linked to thymoma that could be an autoimmune phenomenon, as myasthenia [1, 2]. Some etiologies are proposed: role of self-reactive T-cells, clonal lymphocyte disorder and anti-erythroblast antibodies [3-5]. Classical symptoms of anemia such as fatigue, weakness, pallor or dyspnea may reveal PRCA. PRCA may be found at time of thymoma diagnosis or may develop several years later [6]. It is usually a non-regenerative, normocytic, or sometimes macrocytic anemia. Bone marrow examination generally shows a normal abundance of myeloid cells and megakaryocytes contrasting with the complete absence of erythroblasts [5, 7]. Published data are essentially case reports with a great variability concerning the time of onset of aplasia, its evolution and management [7, 8]. Therapeutic options consist of supportive treatments (iterative transfusions, erythropoietin [EPO]), Immunosuppressive/immunomodulatory treatments (corticosteroid therapy, cyclosporin...) or oncological treatments (thymectomy, radiotherapy, chemotherapy) [8, 9].

Based on an illustrative clinical case, we conducted a systematic review of the literature on the management of thymoma-associated PRCA. Its main objective is to evaluate the impact of thymoma treatment on the therapeutic management of PRCA. The Jules Bordet Institute's ethics committee approved the research protocol on 6/12/2018. (Reference CE 2921).

2. Clinical Case:

A 51-year-old woman was referred for management of a stage IVa B1 thymoma, discovered incidentally on a chest X-ray. Her past medical history is limited to an operated leiomyosarcoma two years before. She neither smoked nor drank and was taking only vitamin D and hormone replacement therapy for menopause.

Initial lab tests were normal including a complete blood count. The tumor was initially unresectable (extensive pleural involvement). Chemotherapy combining cisplatin, adriamycin, cyclophosphamide was started. After the third cycle, the patient presented a mild regenerative anemia with hemoglobin (Hb) level at 10.2 g/dl which was attributed to chemotherapy. She received a subcutaneous injection of EPO (epoetin alpha 40000UI/week). After the fourth cycle of chemotherapy, a morphological and metabolic response of the thymoma was demonstrated. Pleuro-pneumectomy was denied by the patient. She was later hospitalized for a cerebral hemorrhage secondary to central venous thrombosis, four weeks after the first EPO injection. The chemotherapy and EPO were stopped.

Six months later, the disease slowly progressed essentially at the pleural level. There was no anemia and no clinical impact for 9 months. The patient refused to resume chemotherapy. Nineteen months after diagnosis, she was admitted for dyspnea (grade 3 according to modified Medical Research Council dyspnea scale) associated with tinnitus and palpitations. The biology showed normocytic anemia at 6.2 g/dl with reticulocytopenia. There was no iron, vitamin B9 or B12 deficiency (Table 1)**.** Serologies for parvovirus B19 were negative. The EPO level was high. The fecal occult blood tests were negative, and a gastroscopy revealed mild chronic gastritis. Subsequently, a bone marrow biopsy showed aplasia of the erythroid lineage without excess blasts, while the myeloid and megakaryocyte lineages remained within norms. The OGATA score was 0, excluding myelodysplasia. Lymphocyte B were absent and the CD4/CD8 ratio was reduced. After collegial discussion with the hematologists, the diagnosis of PRCA secondary to the thymoma was retained [7]; a possible responsibility of erythropoietin administration was considered unlikely. The patient was transfused with red blood cells several times in view of the symptoms (Figure 1).

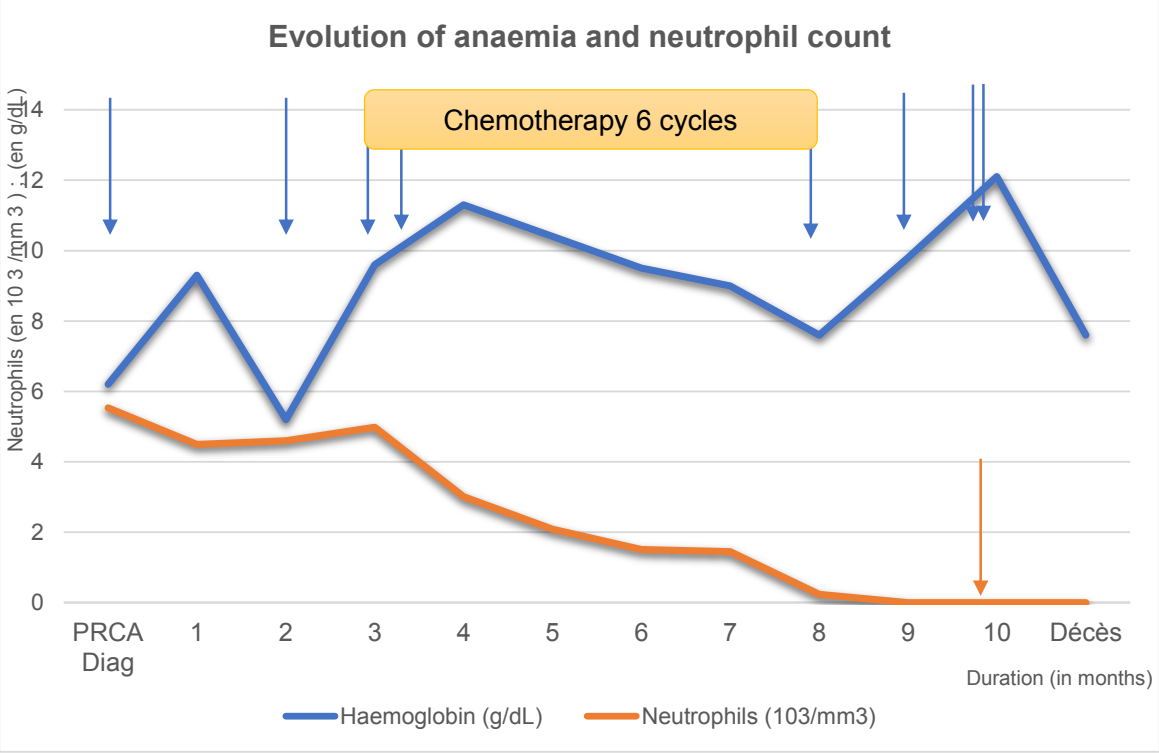
Three months later, the patient agreed to resume cisplatin-adriamycin-cyclophosphamide. In parallel with tumor regression, the patient became transfusion-

Table 1: General laboratory analyses

Laboratory	At Diagnostic of PRCA	At bicytopenia	Reference values
Hemoglobin	6.2	9.8	12-16 g/dl
MCV	94	94	80-100 fL
Reticulocytes	$4x10^3$	$45.8x10^3$	$22.5\text{-}147x10^3/\mu L$
Haptoglobin	162	/	30-200 mg/dL
Ferritin	519	2060	30-350 µg/L
Serum iron	182	18	50-170 µg/dL
Transferrin	225	116	250-380 mg/dL
Tf saturation	58	11	15-50%
Vitamin B9	7.5	12.5	> 4.6 µg/L
Vitamin B12	388	659	197-771 ng/L
CRP	38	175.6	< 10mg/L
Erythropoietin	2453	/	1-9 U/L
Leukocytes	12280	1790	3500-11000/µL
Neutrophils	$5.53x10^3$	0	1.5-6.7x10/µL
Monocytes	$0.25x10^3$	$0.07x10^3$	$0.2\text{-}1x10^3/\mu L$
Basophiles	0	0	$<0.1x10^3/\mu L$
Eosinophils	0	0	$<0.4x10^3/\mu L$
Lymphocytes	$6.51x10^3$	$1.72x10^3$	$1.2\text{-}3.5x10^3/\mu L$
Platelets	$345x10^3$	$301x10^3$	$150\text{-}440x10^3$/microL

Abbreviations: CRP, C reactive protein; MCV, mean corpuscular volume; Tf , transferrin.

Figure 1: Clinical case graph on the evolution of anemia and neutrophil count over time



Blue arrow = transfusion concentrated red blood cells; Orange arrow = filgrastim injection.

Abbreviations: Diag, diagnosis; Hb, hemoglobin; PMN, neutrophils.

independent for 5 months and partially controlled anemia between 9 and 11 g/dl during chemotherapy cycles 2 to 5. After the latter cycle, the patient had to be transfused again due to recurrence of anemia symptoms. At that time, it was difficult to distinguish whether this recurrence is secondary to the chemotherapy or to the PRCA relapse.

At the end of the 6th course of chemotherapy (Adriamycin cumulative dose 316 mg/m²), the patient was hospitalized for febrile neutropenia. There was no tumor recurrence at chest scanner. The blood count showed a persistence of anemia at 9.8 g/dl and a complete absence of neutrophils. A new bone marrow aspiration showed a hypocellular bone marrow containing only a few megakaryocytes. There were no abnormal cells, no plasmocytes and a normal CD4/CD8 ratio without B lymphocytes. A bone marrow biopsy showed no evidence of leukemia, thymoma invasion or macrophage activation syndrome (MAS). Under antibiotic therapy, the patient improved progressively. She received red blood cells transfusions, and 6 injections of filgrastim with no effect on neutropenia. Three weeks later, the patient presented a new episode of febrile neutropenia with positive blood cultures for *Serratia marcescens*. Clinically, the patient presents a vesicular rash suspicious of zona and we start Aciclovir. The patient never presented mucosal lesions, making a Steven Johnson syndrome unlikely. Despite a quick improvement of skin lesions and broad-spectrum antibiotic, the patient deteriorate continuously. A new marrow aspiration showed low cellularity with almost exclusive presence of T-lymphocytes (97%) without phenotypic abnormalities. A macrophagic activation syndrome was suspected in the face of an elevation of the CD25a marker, hyperferritinemia, hypertriglyceridemia, bicytopenia and pyrexia [10] but no hemagophagocytosis was seen at bone marrow aspirate. This bicytopenia could also correspond to a paraneoplastic syndrome as a progression of the thymoma was seen. The patient denied additional investigations and treatment with etoposide-dexamethasone. Palliatives cares were provided. The patient died in a context of multi-organ failure with persistent bicytopenia, blood transfusions dependency and

candidemia (*C. tropicalis*), despite caspofungin and broad-spectrum antibiotics. The family refused an autopsy.

3. Materials and methods

We performed a systematic review of the literature on autoimmune PRCA associated with thymoma. The literature search was conducted using the PICO (Population, Intervention, Comparator, Outcome) technique for the formulation of the research equation: P = Patients with PRCA secondary to a thymoma; I = anti-tumor treatment (systemic, radiotherapy, surgery); C = iterative transfusions of red blood cells; O = resolution of anemia.

The corresponding research criteria of "P" were translated into MeSH terms, and free-text keywords that were searched for in title and abstracts. An experienced medical scientific librarian performed literature search in December 2019 using the Medline database via the OvidSP interface. This research equation was adapted for use in the Scopus database. A first selection based on the title and the abstract content was made by independent double reading by two authors (BL and TB). Articles selected by at least one of the two readers were retained for full reading.

Selections criteria were: language accessible to the reader (French, English, Dutch, Spanish, Italian), clinical case or case series, prospective or retrospective study, systematic review or meta-analysis, evaluation of the therapeutic management of PRCA associated with thymoma and individual case data available. The research was supplemented by screening the references of the selected articles. There was no selection based on the year of publication.

The following variables were collected from each eligible article: age, sex, performance status, thymoma characteristics (Histologic and stage classifications,), thymoma treatment (surgery, chemotherapy, radiotherapy, multimodal) and response to treatment, time of PRCA onset (at diagnosis of the thymoma or the current therapeutic line), assessment and biological

characteristics of anemia (iron, B9, B12, parvovirus B19, Hb level, reticulocytes, EPO, myelogram…), other blood cell dysfunction (platelets, white blood cells), other paraneoplastic syndrome (myasthenia gravis, Good's syndrome ...), PRCA treatment and its response, evolution of the thymoma compared to PRCA, eventual death and its etiology. The PRCA evolution on treatment was arbitrarily classified into three categories: complete remission (CR) for return to normal hemoglobinemia, partial remission (PR) for persisting anemia not requiring transfusion as opposed to transfusion dependence of persistent disease (PD).

Descriptive statistics are limited to mean and median calculations performed with "Excel" software**.**

4. Results

Overall (figure 2), 136 articles were retained, including 119 case reports and 17 case series, published between 1950 and 2019. Three case series were excluded: a Japanese national cohort [11], a French observational study [12] and an American cohort [13] because they overlapped with selected clinical cases described more precisely in other publications. WE found one old systematic review [14]; we retained its illustrative clinical case, but the other bibliographical references cannot be retrieved.

For each clinical case, all the therapeutic lines were evaluated individually (table 2 in appendix). PRCA diagnoses were reported by identifying the time of occurrence in relation to the therapeutic line and the status of the thymic disease. Overall, there were 185 clinical cases corresponding to 312 therapeutic lines.

PRCA occurred most frequently at thymoma diagnosis (111/185). Sixty-two PRCA occurred after a median thymic disease duration of 36 months. In 12 cases, PRCA was diagnosed before thymoma discovery (Table 2 in appendix).

Figure 2: Flow chart

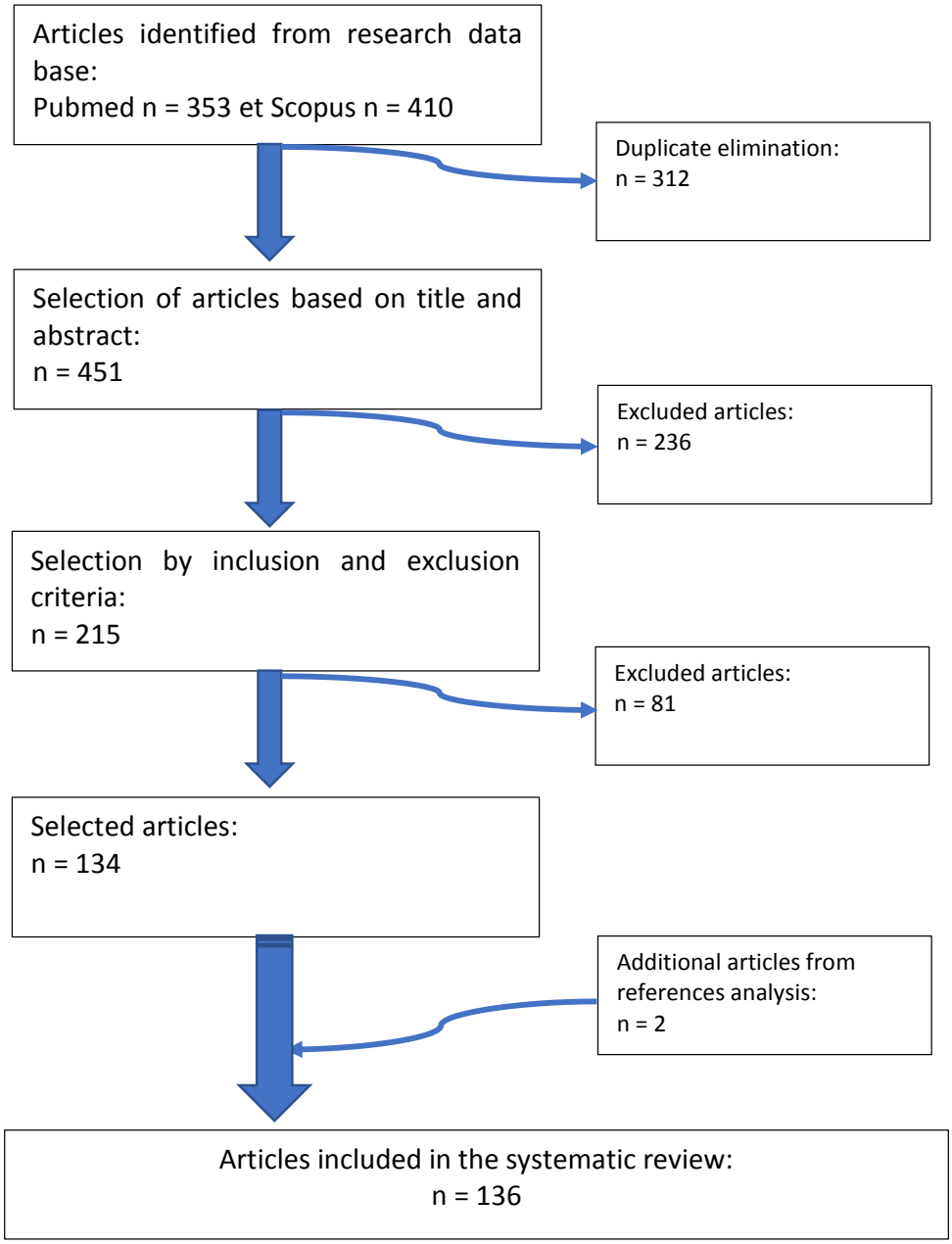


Table 3: PRCA responses in function of the treatment applied

Therapeutic sequence	CR	PR	PD
Anti-tumor treatment:			
- **Thymectomy**	**23**	**6**	**50**
- **Thymectomy + Chemotherapy**	**2**	**-**	**1**
- **Thymectomy + Radiotherapy**	**4**	**1**	**4**
- **Thymectomy + Chemotherapy + Radiotherapy**	**-**	**-**	**1**
- **Chemotherapy**	**-**	**1**	**3**
- **Radiotherapy**	**-**	**-**	**1**
- **Chemotherapy + Radiotherapy**	**-**	**-**	**1**
- **Total**	**29**	**8**	**61**
Treatments acting on the immune system:			
- **Corticosteroids**	**25**	**5**	**31**
- **Cyclosporin**	**23**	**3**	**5**
- **Cyclophosphamide**	**2**	**-**	**2**
- **Azathioprine**	**1**	**-**	**2**
- **Others IST unspecified**	**6**	**-**	**2**
- **Other monotherapy***	**8**	**5**	**14**
- **Corticoids + Cyclophosphamide**	**9**	**1**	**7**
- **Corticoids + Cyclosporin**	**3**	**-**	**4**
- **Others combinations**	**4**	**4**	**15**
- **Total**	**81**	**18**	**82**
Combination of anti-tumor treatment and treatments acting on the immune system:			
- **Thymectomy + Corticoids**	**6**	**4**	**2**
- **Thymectomy + Combination IST**	**3**	**1**	**1**
- **Thymectomy + Corticoids + Cyclosporin**	**1**	**-**	**-**
- **Chemotherapy + Combination IST**	**2**	**-**	**2**
- **Chemotherapy + Radiotherapy + Corticoids**	**-**	**-**	**1**
- **Radiotherapy + Combination IST**	**1**	**4**	**1**
- **Total**	**13**	**9**	**7**

Numbers are presenting the number of patients in each category

**adrenocorticotropic hormone; androgens; rituximab; splenectomy; anti-thymocytes globulins; immunoglobulins; bone marrow allograft; plasmapherese.*

IST, Immunosuppressive treatments

Table 3 summarizes the response of PRCA according to the applied treatment, divided into three groups (anti-tumor treatment, immune-mediated treatment, or a combination of the two approaches). Overall, tumor treatments resulted in 29.6% CR. Thymectomy alone or in combination with other therapies showed a 31.5% CR rate, whereas chemotherapy and/or radiotherapy without thymectomy showed quite none. Treatments acting on the immune system showed a CR rate of 45%, 74% with cyclosporine compared to 41% after corticosteroids. Corticosteroid-cyclophosphamide and corticosteroid-cyclosporin combinations have CR rates of 53% and 43%. Combination treatments of anti-tumor treatment and treatments acting on the immune system have a CR rate of 45%. Combinations including thymectomy had a 56% CR rate versus 27% CR for combinations without thymectomy.

Table 4: PRCA responses according to the type of thymic resections:

Type of resection:	Complete	Incomplete	No
PRCA responses:			
- **Complete remission**	**82 (58%)**	**4 (40%)**	**16 (55%)**
- **Partial Remission**	**14 (10%)**	**2 (20%)**	**4 (14%)**
- **Persistent disease**	**45 (32%)**	**4 (40%)**	**9 (31%)**
- **Total**	**141**	**10**	**29**

This table shows the response of PRCA depending on the type of thymic resections. Complete thymic resections appear to have better CR rate than incomplete resections.

When PRCA persisted after thymectomy remission was essentially achieved with immunomodulatory treatments. Overall PRCA complete remission rate in these cases PRCA persistence post-thymectomy are approximately 50% regardless of the treatment line applied (Table 5).

Complete remission

of PRCA was associated in 70% of cases with thymic CR while persistent PRCA (PD) does not appear to be associated with progressing thymoma (Table 6).

Table 5: PRCA rescue therapy and responses in case of PRCA persistence post-thymectomy

2nd line (N=44)*		3rd line (N=17)		More than 3 lines (N=11)	
Chemotherapy	1 PD	Allograft	1 CR 1 PR	Corticoids	2 CR 1 PD
Corticosteroids	7 CR 8 PD	Corticosteroids	2 CR 1 PD	Cyclosporine	2 CR 1PD
Cyclosporin	3 CR 2 PR	Cyclosporin	3 CR	Immunoglobulins	1 PR
CPA	2 PD	Immunoglobulins	1 PD	Others IST	1 CR
Azathioprine	1 CR	ATG	1 PD	Combinations	2 PD
Androgens	1 CR 2 PD	Androgens	1 PD	ACTH	1 CR
Others IST	3 CR	Splenectomy	1 CR 1PD		
Combinations	6 CR 1PR 7PD	Combinations	2 CR 2PD		

Abbreviations: CPA, Cyclophosphamide; ATG, antithymocyte globulins; IST, Immunosuppressive treatments, ACTH ; Adrenocorticotropic hormone.

PRCA response according to Masaoka stage could be assessed in 46 cases; there were 15 CR out of 29 stage I or II and 9 CR out of 17 stage III and IV thymoma ($p = 0.94$). Also, we did not observe any influence of histology with 10 CR out of 26 cases for types A, AB and B1 and 7 CR out of 11 cases in types B2 and B3 ($p = 0.15$).

The median duration of PRCA CR was 18 months after immunomodulatory treatment versus 15 months after anti-tumor treatment alone or in combination with an IST treatment. There was no effect of PRCA onset and CR, with 60% versus 55% CR when PRCA occurred at thymoma diagnosis or during the course of the disease. Five cases of spontaneous remission were observed and an average of 1.7 PRCA flare-ups (persistence/worsening despite treatment) were identified per patient.

Twenty-one relapses of PRCA were identified including only five in parallel to the thymic relapse. There were 58 reported deaths. Eight are directly attributable to thymic progression. The majority (n=36) are secondary to PRCA treatment with infectious origin

(n=25 including 20 on immunomodulatory therapy) and 6 in the context of systemic hemosiderosis.

Table 6 PRCA's response according to the status of the thymoma

PRCA's response	Progressive status of thymoma
Complete remission : **106**	Complete remission : **74** Partial remission : 5 Stable Disease: 5 Progressive Disease: 13 No information : 9
Partial remission: **23**	Complete remission : 14 Partial remission: **1** Stable disease : 1 Progressive disease: 4 No information : 3
Persistent disease: **51**	Complete remission : 23 Partial remission: 4 Stable disease: 4 Progressive disease: **15** No information : 5

5. Discussion

We present an illustrative clinical case of PRCA diagnosed during the course of stage IVA thymoma, with parallel PRCA and thymoma partial remission during chemotherapy. A systematic review was conducted in order assessing the best therapeutic option for controlling this rare paraneoplastic syndrome.

Thymectomy is the therapeutic cornerstone for thymoma, whatever alone or in a multimodal approach. It is also the main antitumoral and the most effective therapeutic option for PRCA, essentially for the first line care of PRCA. Only six documented cases were treated

only with chemotherapy and/or radiotherapy with only one reported PR. Our clinical case corresponds to a very rare situation of PRCA partial response with chemotherapy alone. The results from the systematic review are supporting the role of thymectomy as a key factor for controlling PRCA [15, 16]. The combination of thymectomy with radiotherapy shows good results (44% of CR, table 3) but this must again be qualified by the low number of cases studied

The better CR rate with a complete thymic resection (Table 4) is only exploratory value as the number of incomplete resections is small. The same observation can be made regarding the comparison between complete thymectomy versus no thymectomy.

Due to the scarcity of the disease, there is no controlled trial comparing therapeutic attitude "with" versus "without" thymectomy. In the present setting, data with thymectomy may be biased by selection of less aggressive thymomas, particularly stages I and II and type A or AB. However, we did not find a difference in the control rate of PRCA depending on Masaoka stage or histological subtypes (A, AB, B1 versus B2 and B3). Our data report a predominance of type B1 thymomas associated with PRCAs represented at 31% against 13% usually in the general population [17]. The value of those analyses is limited by the low number of published cases and the changes in classifications over time [18].

Treatments with immunomodulatory action, mainly cyclosporin and corticosteroids demonstrated in this systematic review their interest in the management of PRCA, whatever in first-line or in case or PRCA recurrence. Japanese [11] and American [13] national cohorts reported similar figures. These results are in contradiction with a French observational study [12] in which corticosteroid were most effective. Finally, combination therapies (anti-tumor + IST) do not show a better efficacy in terms of CR rate than immunomodulatory treatments but

do expose to an increased risk of side effects, whereas an anti-tumor treatment alone may be sufficient in one third of cases.

The PRCA onset is generally at thymoma diagnosis while one-third occurred later. Most of the clinical cases (158/185) were confirmed by a bone marrow aspiration. As for all retrospective analyses, and particularly here as the data records are done on a very large time period, it is not possible going back to the initial data. So, we may only consider the diagnosis provided by the authors of the case reports. Our case occurred concomitantly with a thymic relapse. Other differential diagnoses were reasonably excluded. PRCA secondary to anti-EPO antibodies is not consistent with high EPO level and PR under chemotherapy [19]. Thymoma bone marrow infiltration or post-anthracycline leukemia were excluded by multiple bone marrow aspiration and biopsy. Infections as parvovirus B19 were negative and the discrete chronic gastritis did not explain such anemia. It is also questionable whether the anemia (6 months prior to PRCA) attributed to the first cycle of chemotherapy is not already representative for the start of PRCA but this anemia responded to EPO and did not recur when chemotherapy was stopped.

The terminal course is marked by the development of bicytopenia (neutropenia-anemia), for which the diagnosis of MAS was suggested due to the presence of both biological (bicytopenia, hypertriglyceridemia, hyperferritinemia, CD25 increased) and clinical (pyrexia and skin lesions) criteria. The H-Score is 169 corresponding to a probability of 78% [10]. The etiology of MAS could be active thymoma or infection. No hemagophagocytosis was seen at bone marrow aspirate and myelogram ruled out leukemia or medullar invasion. Nevertheless, the low cellularity should suggest a relapse of PRCA coupled with paraneoplastic neutropenia. Approximately 10 cases of white blood cell aplasia secondary to thymoma have been described and could be treated by thymectomy or immunosuppression [20]. There were also five cases in the French cohort [12]. No association of PRCA and agranulocytosis was found in the literature.

In our systematic review, there were only two cases of leukopenia associated with PRCA, but they did not show neutropenia. However, the association PRCA with amegacaryocyte thrombocytopenia was described and there are more than ten cases in our systematic review. Finally, two cases of pancytopenia were reported but without neutropenia. A systematic review of the few cases of pancytopenia associated with thymomas was suggesting a therapeutic role for immunosuppressive drugs [21].

In our systematic review, we observed that complications secondary to PRCA treatment are representing the largest cause of death, particularly by infection secondary to immunosuppression. Other authors found the same findings with cyclosporin and recommended careful monitoring of patients undergoing IST treatment [11]. The French review even suggests the use of rituximab to avoid immunosuppression based on their two cases of CR out of 4 treated [12]. However, there was only one case treated with rituximab in our review showing PR.

This systematic review has some limitations. The data reported in the selected clinical cases are very heterogeneous, particularly with regard to thymic characteristics (stage and type, duration and type of treatment, type of response), PRCA (diagnostic means, duration and type of treatment, duration and type of response) and patient follow-up (duration of follow-up, possible cause of death). Criteria for PRCA remission are based on the normal hemoglobin level and independence from transfusion but do not take into account the duration or decrease in frequency of transfusion. We defined arbitrarily these criteria in the absence of literature consensus. Corticosteroid was considered by default as treatment for PRCA except when explicitly described as an anti-tumor therapy. We did not select foreign language articles that were inaccessible to readers: sixty articles in Japanese, four in German, two in Korean, two in Chinese, one in Danish and one in Russian were excluded while some Japanese articles

translated into English from other journals were retained. Finally, the analysis by therapeutic line does not reveal the influence of previous therapies on the final PRCA control.

6. Conclusion:

In this systematic review, thymectomy appears to be the most effective anti-tumor therapy for PRCA associated thymoma. Other anti-tumor treatments may induce partial remissions, but no case of complete remission was reported. If PRCA persists after thymectomy, immunomodulatory therapy should be considered with cyclosporin having the best CR, taking into account the risk of infectious complications. The respective place of anti-tumor and immunomodulatory treatments for PRCA, or their combination must be validated in prospective clinical studies.

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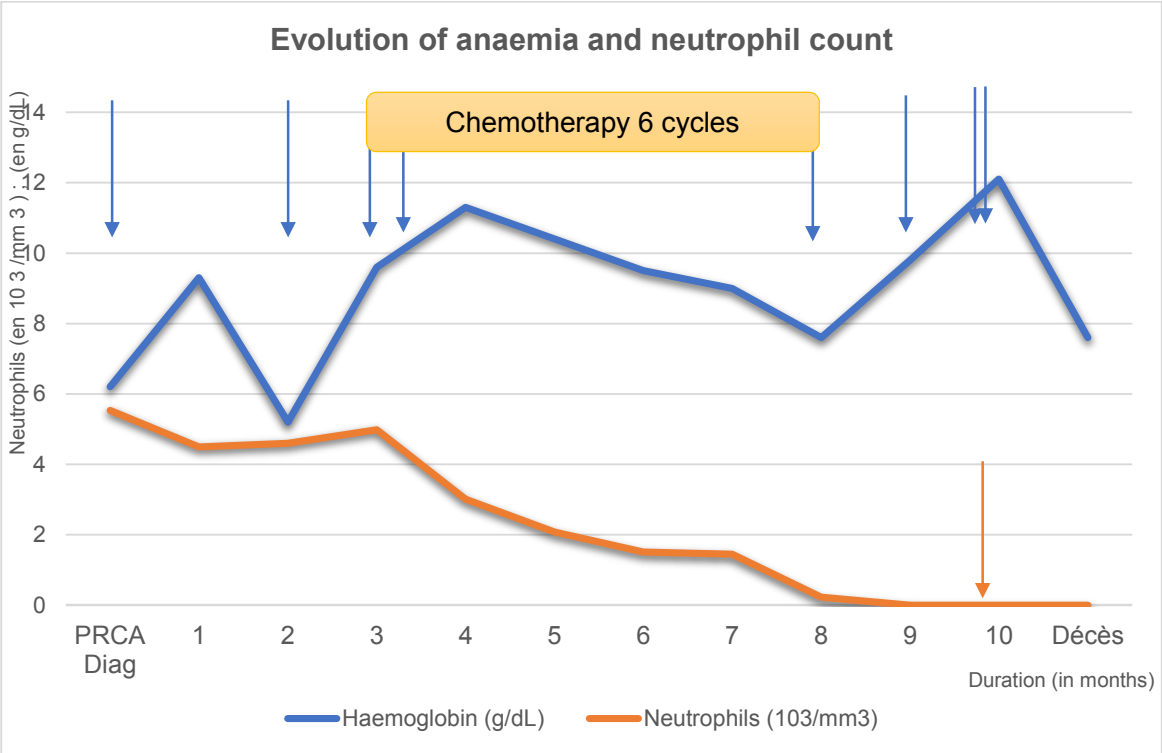
Figure 1: Clinical case graph on the evolution of anemia and neutrophil count over time



Blue arrow = transfusion concentrated red blood cells; Orange arrow = filgrastim injection.

Abbreviations: Diag, diagnosis; Hb, hemoglobin; PMN, neutrophils.

Figure 2: Flow chart

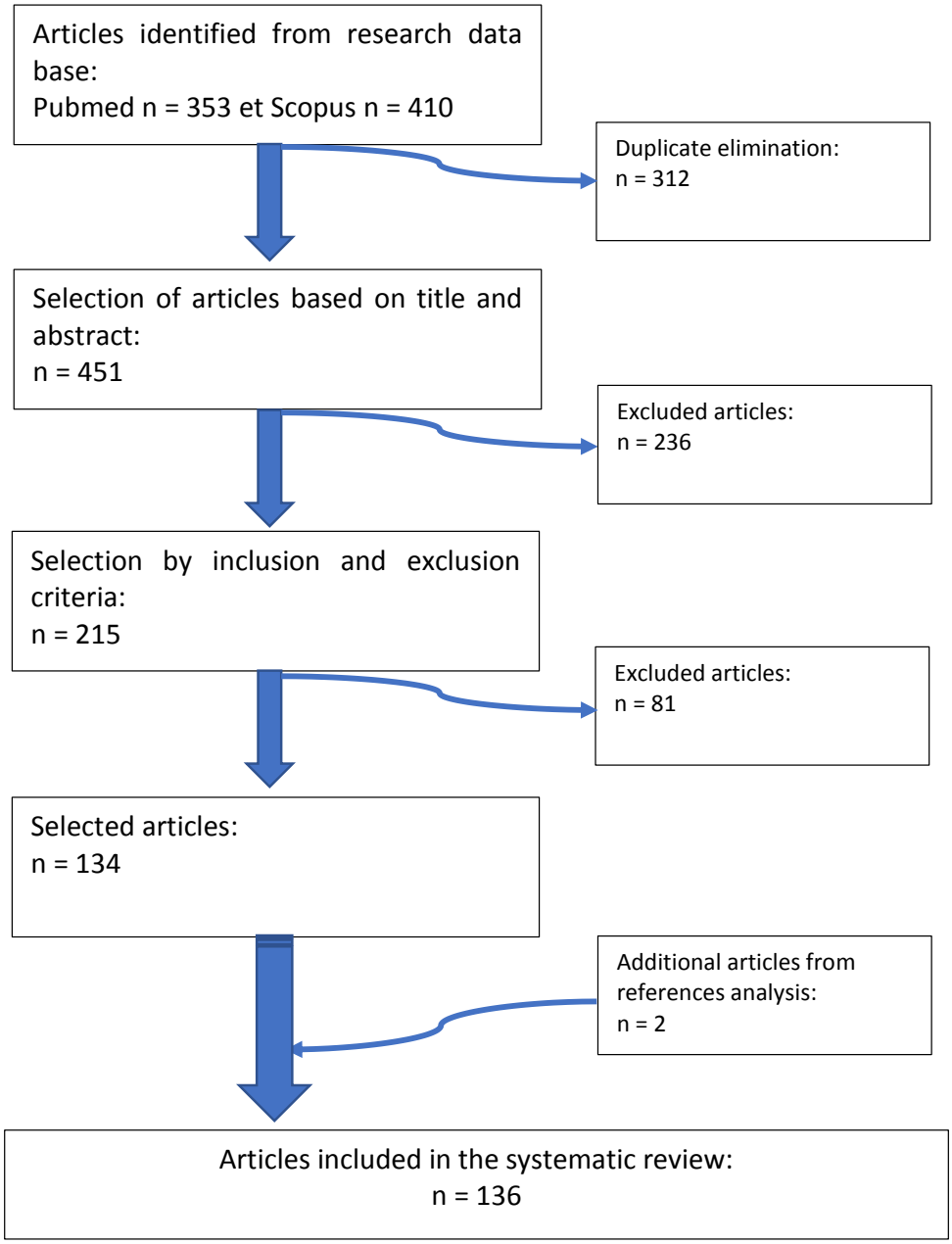


Table 1: General laboratory analyses

Laboratory	At Diagnostic of PRCA	At bicytopenia	Reference values
Hemoglobin	6.2	9.8	12-16 g/dl
MCV	94	94	80-100 fL
Reticulocytes	$4x10^3$	$45.8x10^3$	$22.5\text{-}147x10^3/\mu L$
Haptoglobin	162	/	30-200 mg/dL
Ferritin	519	2060	30-350 µg/L
Serum iron	182	18	50-170 µg/dL
Transferrin	225	116	250-380 mg/dL
Tf saturation	58	11	15-50%
Vitamin B9	7.5	12.5	> 4.6 µg/L
Vitamin B12	388	659	197-771 ng/L
CRP	38	175.6	< 10mg/L
Erythropoietin	2453	/	1-9 U/L
Leukocytes	12280	1790	3500-11000/µL
Neutrophils	$5.53x10^3$	0	1.5-6.7x10/µL
Monocytes	$0.25x10^3$	$0.07x10^3$	$0.2\text{-}1x10^3/\mu L$
Basophiles	0	0	$<0.1x10^3/\mu L$
Eosinophils	0	0	$<0.4x10^3/\mu L$
Lymphocytes	$6.51x10^3$	$1.72x10^3$	$1.2\text{-}3.5x10^3/\mu L$
Platelets	$345x10^3$	$301x10^3$	$150\text{-}440x10^3/microL$

Abbreviations: CRP, C reactive protein; MCV, mean corpuscular volume; Tf , transferrin.

Table 2: Clinical cases of thymoma associated PRCA distributed by therapeutic lines

Reference	Year of parution	Age /sex	PRCA pre-treatment	Timing of onset PRCA	PRCA treatment	Outcome
Parry[1]	1950	71/M	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease 6W Death in CR 1,5M
Chalmers[2] ***(SC)***	1954	48/M	None	Concomitant	1. ACTH 2. Thymectomy 3. Splenectomy 4. ACTH	PD some months? CR 6W -> Relapse PD follow-up? CR 2 years
		62/W	None	9 months before Thymoma	1. Thymectomy 2. ACTH 3. Corticoids/Iron/Vitamins 4. Splenectomy 5. ACTH -> ACTH Long view	Persistent Disease 6W Persistent Disease 1M Persistent Disease 1M Persistent Disease 1,5M Relapse 4M -> CR 2M
Kurrein[3]	1959	70/W	None	2 years after Thymoma	Corticosteroids	Death in PD 1,5 months
Siguier[4]	1959	66/W	None	Concomitant	Thymectomy	Death in PD 6 months
Freeman[5]	1960	74/M	None	Concomitant	Thymectomy	Death in PD 4 months
Bernard[6]	1962	76/M	None	5 years after Thymoma	Corticosteroids 1M -> Cort Long View	Relapse 2 months -> CR
Jahsman[7]	1962	77/M	None	Concomitant	1. Thymectomy 2. Corticosteroids + Androgens	Persistent Disease Death in PD 19 months
Andersen[8]	1963	58/M	Thymectomy + Radiotherapy	2 years after Thymectomy/Rxpy	1. ACTH 2. ACTH/Iron-> Corticosteroids 3. Spontaneous remission	CR 4 Years -> Relapse Persistent Disease 9Y CR hindsight 2 years
Radermecker[9]	1964	59/W	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease 5M CR hindsight 9 months
Kinoshita[10]	1966	67/M	None	Concomitant	1. Thymectomy 2. Corticosteroids	Partial remission 1M CR hindsight 1 year
Baudouin[11]	1968	75/M	None	Concomitant	Corticosteroids	Death in PD 3 months
Hamilton[12]	1969	32/W	None	Concomitant	1. Radiotherapy 2. Corticosteroids 6 months	Persistent Disease CR hindsight 2 years

Pizzuto[13]	1969	73/M	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease Death in PD
Siguier[14]	1969	60/W	None	Concomitant	Corticosteroids -> Thymectomy	CR hindsight 2 years
Souquet[15]	1970	55/M	Surgery-> Rpse22Y: Cort + Ctp: PD-> Cort + Rxpy	After Radiotherapy	Corticosteroids + Androgens ACTH	PD PRCA (PR Thy) Death in PD 7 months
AlMondhiry[16]	1971	32/W	None	Concomitant	Thymectomy	CR hindsight 3 months
Bernadou[17]	1972	75/W	None	Concomitant	Radiotherapy + Corticosteroids + Androgens	Death in PR 3 months
Leménager[18]	1972	60/W	None (autopsy diagnosis)	2 months before the death	Corticosteroids -> Chemotherapy	Death in PD 2 months
Lenormand[19]	1972	56/W	None	Concomitant	1. Thymectomy 2. Androgens 3. Corticosteroids + Androgens	Persistent Disease 1M Persistent Disease 4M Death in CR 18 months
Fieschi[20]	1973	68/W	None	Concomitant	Thymectomy	Death in CR 8 years
Le Brigand[21]	1973	48/W	None	Concomitant	Thymectomy -> Radiotherapy	CR hindsight 2 years
Marmont[22]	1973	60/M	None	Concomitant	Corticosteroids + CPA -> Cort LV	Death in CR
Vasavada[23]	1973	67/W	None	Concomitant	1. Thymectomy 2. Androgens	Persistent Disease 1M Death in PD 4 months
Takigawa[24]	1974	49/W	None (autopsy diagnosis)	1 month before the death	Corticosteroids + Androgens	Death in PD 1 month
Desevilla[25]	1975	64/M	Radiotherapy (PR)	18 months after radiotherapy	1. Cyclosporine + Corticosteroids	Persistant Disease
Geary[26]	1975	56/M	Thymectomy	1 year after Thymectomy	1. Androgens 2. Corticosteroids + 6MP 3. Corticosteroids -> Androgens -> 6MP	Persistent Disease 1M Persistent Disease 2M Death in PD 3M
Dujardin[27]	1976	78/M	None	Concomitant	Thymectomy + Corticosteroids + And	Death in PD
Marín[28] ***(SC)***	1976	60/W	None	6 years after thymoma	1. Thymectomy 2. Androgens	CR 7 months -> Relapse Death in CR 21 months
		75/W	None	Concomitant	Thymectomy	Death in PD
Albahary[29]	1977	79/M	None	9 years after Thymoma	Corticoids 2 months	CR hindsight ?
Robins-Browne[30]	1977	62/M	None	Concomitant	Thymectomy	CR hindsight 21M
Houghton[31]	1978	51/M	None	Concomitant	Corticoids Long View	CR with Cort hindsight?

Kurstjens[32]	1978	67/M	None	Concomitant	1. Thymectomy 2. Corticosteroids + Cyclophosphamide 3. Splenectomy 4. Corticosteroids long view	Persistent Disease 6W Persistent Disease 2M CR 1 year -> Relapse CR 2 years
Pic[33]	1978	72/W	None	Concomitant	Thymectomy	PD hindsight 3W
Varet[34]	1978	63/W	Thymectomy	1 month after Thymectomy	1. Corticosteroids 1 month 2. Cyclophosphamide 3 months	Persistent Disease 1M CR hindsight 4 years
Zeok[35] ***(SC)***	1979	58/M	None	Concomitant	Thymectomy-> Radiotherapy	Death PD 6M
		61/M	None (Ct normal)	9 months before diagnosis of Thymoma	1. Chemotherapy 2. Thymectomy 3. Splenectomy	Persistent Disease 9M Persistent Disease 6M Death in PD
		69/M	None	Concomitant	Thymectomy	CR hindsight 16 months
Bourgeois[36]	1981	76/M	None	Concomitant	Plasmapheresis	Death in PR 2 years
Earlywine[37]	1981	67/M	None	Concomitant	Thymectomy	CR hindsight 1 year
Tiber[38]	1981	48/M	Chemotherapy (2) + Cort -> Chemotherapy (3)	After 3rd cycle of chemotherapy	Androgens + Corticosteroids + Chemotherapy long view	CR hindsight 2,5 months
Sharma[39]	1982	55/M	None	Concomitant	1. Thymectomy 2. Cyclophosphamide 3. Androgens 4. Corticosteroids	Persistent Disease Persistent Disease Persistent Disease PD hindsight 4 months
Shibata[40]	1982	60/M	Radiotherapy	After radiotherapy	1. Thymectomy 2. Androgens 3. IST (Cort/CPA/Aza/And)	Persistent Disease 2M Persistent Disease 1M Persistent Disease
Frau[41]	1983	40/W	Chemotherapy	After chemotherapy	CPA + Corticosteroids + Radiotherapy	Death thy/PR 18 months
Socinski[42]	1983	72/W	None (Ct normal-> Diag autopsy)	9 months before death	CPA + Corticosteroids-> Cort long view	Death in CR 3 months
Milnes[43]	1984	64/M	None	Concomitant	1. Thymectomy 2. Corticosteroids + Cyclophosphamide	Persistent Disease CR hindsight 1 year
Estivill[44] ***(SC)***	1985	77/W	None	Concomitant	1. Thymectomy 2. Chemotherapy 3. Corticosteroids long view	PR 2/3 months Persistent Disease CR hindsight 1 month

		65/M	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease CR hindsight 8 months
Jootar[45]	1985	55/W	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease CR with Cort hindsight?
Levinson[46]	1985	56/M	None	Concomitant	1. Thymectomy 2. Corticosteroids + Cyclophosphamide	Persistent Disease 3M CR hindsight 3 months
Soler[47]	1985	72/W	None	Concomitant	Corticosteroids long view	CR hindsight ?
		79/W	None	Concomitant	Corticosteroids	Death in CR under Cort
Eridani[48]	1986	61/W	None	Concomitant	1. Thymectomy 2. Azathioprine 3. Spontaneous remission	Persistent Disease 4M Persistent Disease CR hindsight 5M
Mangan[49]	1986	80/W	None	6 years after thymoma	Corticosteroids + CPA-> Cort long view	Death thy/CR PRCA
Bailey[50]	1988	88/M	None	Concomitant	Corticosteroids	Death in PD 5 years
Masaoka[51]***(SC)***	1989	45/W	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease Persistent Disease
		58/M	None	Concomitant	Radiotherapy + Corticosteroids	Complete Remission
		58/M	None	Concomitant	1. Corticosteroids 2. Thymectomy -> Corticosteroids	Persistent Disease Complete remission
		58/W	None	Concomitant	1. Corticosteroids 2. Thymectomy -> Corticosteroids	Persistent Disease Complete Remission
		65/W	None	Concomitant	Thymectomy	Persistent Disease
		67/M	None	Concomitant	1. Corticosteroids 2. Thymectomy -> Cort + Azathioprine	Persistent Disease Complete Remission
		68/W	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease Persistent Disease
		69/W	None	Concomitant	1. Corticosteroids 2. Thymectomy -> Cort + Azathioprine	Persistent Disease Complete Remission
		69/W	Thymectomy -> Rxpy	After radiotherapy	Spontaneous Remission	Complete Remission
		78/W	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease Persistent Disease
		46/W	None	Concomitant	Thymectomy	Death in PD

		47/M	None	Concomitant	1. Corticosteroids 2. Thymectomy-> Corticosteroids + And	Persistent Disease Death in CR 13 years
		59/W	None	Concomitant	1. Thymectomy 2. Corticosteroids + Azathioprine	Persistent Disease Death in PD
		59/M	None	Concomitant	1. Corticosteroids 2. Thymectomy-> Corticosteroids	Persistent Disease Death in CR
		60/M	None	Concomitant	Thymectomy	Death in PD
		63/M	None	Concomitant	Thymectomy	Death in PD
		71/M	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease Death in PD
Blumsohn[52]	1990	65/W	None	Concomitant	1. Thymectomy 2. Cyclosporine	Persistent Disease 8M PR hindsight 2 month
Ito[53]	1991	57/W	None	Concomitant	Thymectomy	CR hindsight 4 month
Liozon[54]	1991	65/M	None	Concomitant	Thymectomy + Cort long view	PR hindsight ?
Fong[55]	1992	60/M	None	4 months before Thymoma	1. Corticosteroids 2. Thymectomy 3. Chemotherapy + Radiotherapy	Persistent Disease Persistent Disease Death in PD
Murakami[56]	1992	56/W	None	Concomitant	1. Corticosteroids 2. Spontaneous Remission 3. Corticosteroids	CR 9Y-> Relapse CR 2Y-> Relapse Death in CR 2 years
Garcia[57]	1993	62/M	None	Concomitant	1. Thymectomy 2. Corticosteroids + Cyclophosphamide 3. Cyclosporine short view -> CSP LV	CR 4M-> Relapse Persistent Disease Complete Remission
Haberhauer[58]	1993	22/W	None	Concomitant	Thymectomy	CR hindsight ?
Garcia Vela[59]	1993	62/M	None	Concomitant	1. Thymectomy 2. Corticosteroids + Cyclophosphamide 3. Immunoglobulin IV 4. Cyclosporine long view	Persitent Disease 1M Persistent Disease Persistent Disease CR 15M under CSP
Victor[60]	1993	46/W	None	Concomitant	1. Thymectomy 2. Corticosteroids + CPA 3M	Persistent Disease 1M CR hindsight 9 months
Adhikari[61]	1994	51/M	None	Concomitant	1. Thymectomy + CPA + Cort 2. Corticosteroids	PR 1A-> Relapse PR 6M-> Relapse

					3. Corticosteroids + Cyclophosphamide	Death in PD 3 months
Handa[62]	1994	73/M	None	Concomitant	Thymectomy	Death in PD 4 months
McManus[63]	1994	41/M	Thymectomy	4th day post-Thymectomy	1. Corticosteroids 2 months 2. Cyclosporine long view	Persistent Disease 2M CR with CSP hindsight ?
Duchmann[64]	1995	66/W	Thymectomy -> Radiotherapy	2 years post-Thymectomy/Rxpy	Corticosteroids long view	Death in PD 3 months
Katabami[65]	1995	53/W	None	Concomitant	1. Thymectomy 2. Corticosteroids + Cyclophosphamide	Persistent Disease CR hindsight ?
Konstantopoulos[66]	1995	35/W	None	Concomitant	Thymectomy	CR hindsight ?
Nishioka[67]	1995	43/M	Radiotherapy + Ctp (2)-> Cort	6 years after diagnosis	Corticosteroids	Death < Acute leucemia
Teoh[68]	1995	58/W	None	Concomitant	Radiotherapy + Cort + CPA 3M-> EPO	Death in PD 15 months
Wong[69]	1995	28/W	None	Concomitant	Thymectomy -> EPO long view	PR hindsight 1 year
Charles[70] ***(SC)***	1996	56/M	Thymectomy	3 mois post-Thymectomie	1. Corticoids -> Cyclophosphamide 2. Corticoids long view	Rpse when stop CPA CR hindsight 5 years
		58/M	None	Concomitant	1. Corticosteroids -> Cyclophosphamide 2. Chemotherapy: VIN 3. Azathioprine 4. Thymectomy 5. Corticosteroids	Persistent Disease Persistent Disease Persistent Disease Persistent Disease CR hindsight 9 years
		57/W	None	Concomitant	Thymectomy	Death in CR 1 month
Masuda[71]	1997	55/M	None	Concomitant	1. Corticosteroids 1month 2. Thymectomy 3. Cyclophosphamide 4. Cyclosporine short view -> CSP LV	Persistent Disease 1M Persistent Disease Persistent Disease 7M Relapse 7 months -> CR
Palmieri[72]	1997	56/W	Chemotherapy 6 cycles	After 3rd Chemotherapy	Corticoids + ACTH long view	PR hindsight 15 months
Di Mario[73]	1998	35/W	Thymectomy (RC thymoma)	11 years after-Thymectomy	1. Corticosteroids 2. Cyclosporine long view	Persistent Disease CR hindsights 7 months
Kashyap[74]	1998	46/W	Thymectomy	6 months post-Thymectomy	Corticosteroids 3 months	CR hindsight 3 years
Liozon[75]	1998	65/M	None	Concomitant	1. Thymectomy 2. Corticosteroids + Cyclosporine -> Ctp	Persistent Disease 3M Persistent Disease 8M

					3. Cyclosporine long view 4. ALG + And -> Azathioprine + IgG IV	CR42M with CSP->Rpse Persistent Disease
Mizobuchi[76]	1998	70/W	None	Concomitant	Thymectomy + Corticosteroids 2 days	PR hindsight 9 months
Sasidharan[77]	1998	44/M	None	Concomitant	Thymectomy	CR hindsight?
Spath-Schwalbe[78]	1998	46/W	Thymectomy	2 years post-Thymectomy	1. Corticosteroids 1 month 2. Cyclosporine long view	Persistent Disease 2M CR hindsight 10M CSP
Kurukulasuri-ya[79]	1999	60/W	None	4 months before thymoma	1. Corticosteroids + Cyclosporine 2. Thymectomy	CR -> 4 months CR no follow up
Ito[80]	1999	57/M	None	Concomitant	1. Corticosteroids + Cyclophosphamide 2. Thymectomy -> Corticosteroids 3. Cyclosporine -> Azathioprine 4. Corticosteroids long view	Persistent Disease 2M PR 2 months -> Relapse Persistent Disease CR hindsight 2 ans
Larroche[81]	2000	75/M	None	Concomitant	1. Thymectomy 2. Corticosteroids 1 year 3. Corticosteroids + ACTH 1month 4. Immunoglobulins IV 5 days	Persistent Disease 1M Persistent Disease 1Y Persistent Disease 1M RP hindsight 21 months
McCune[82]	2000	47/M	Thymectomy	6 weeks post-Thymectomy	1. Corticosteroids 2. Cyclosporine long view	Persistent Disease Death in CR 2 years
Kuo[83] ***(SC)***	2001	62/M	None	Concomitant	1. Thymectomy 2. Immunosuppressants 3. Immunosuppressants 4. Immunosuppressants	Persistent Disease 3M CR 3 years -> Relapse CR 1 year 6M-> Relapse CR hindsight 2 years
		29/W	None	Concomitant	1. Thymectomy 2. Immunosuppressants	Persistent Disease 3M CR -> 2,5 years
		53/W	None	Concomitant	1. Thymectomy 2. Immunosuppressants	Persistent Disease 3M CR -> 1year, 5 months
		44/M	None	Concomitant	Surgery -> Radiotherapy + Ctp	PD -> 22 months
		41/W	Chemotherapy -> Surgery	1 year after Chemotherapy/Surgery	1. Immunosuppressants 2. Immunosuppressants	CR -> Relapse Death in PD 2,5 years
Poullis[84]	2001	60/M	None	Concomitant	Corticosteroids-> Thymectomy	PR hindsight 6 months
Samaiya[85]	2001	58/W	None	Concomitant	1. Thymectomy + Corticosteroids 2. Corticosteroids	CR-> Relapse (Cort stop) Persistent Disease

					3. Cyclosporine	CR with CSP hindsight ?
Lahiri[86]	2002	43/M	None	Concomitant	Thymectomy + Corticosteroids LV	PR hindsight 10 months
Murakawa[87] ***(SC)***	2002	31/W	None	Concomitant	1. Thymectomy 2. Corticosteroids	Persistent Disease Death in PD 7 months
		39/M	Thymectomy	8 years post-Thymectomy	Corticosteroids	Death in PD 123 months
		50/W	Thymectomy	Post-Thymectomy	Chemotherapy + Radiotherapy + Cort	Death in PD 67 months
		48/W	None	Concomitant	Thymectomy	CR hindsight 12 years
		70/W	Thymectomy	4 months post-Thymectomy	Corticosteroids + Cyclophosphamide	Death in PD 11 months
		64/W	None	Concomitant	1. Thymectomy + Radiotherapy 2. Corticosteroids	Persistent Disease CR hindsight 11 months
Suzuki[88] ***(SC)***	2003	51/W	Thymectomy	Post-Thymectomy	Cyclosporine	PD follow-up ?
		46/M	Thymectomy -> Ctp + Rxpy	Post-Chemotherapy/Radiotherapy	Cyclosporine	CR follow-up?
		62/W	Thymectomy -> Ctp + Rxpy	Post-Chemothérapy/Radiotherapy	Cyclophosphamide	CR follow-up ?
		69/W	Thymectomy	Post-Thymectomy	Azathioprine	CR follow-up ?
Dhaliwal[89]	2004	51/W	None	Concomitant	Thymectomy -> Radiotherapy	CR hindsight 1Y
Fujiu[90]	2004	36/W	Ctp->Thymectomy +Rpy	9 mois post-Thymectomy/Rxpie	Cyclosporine	CR hindsight 3M
Maeda[91]	2004	88/W	None	Concomitant	1. Thymectomy 2. Cyclosporine + EPO	Persistent Disease CR hindsight 11M
Suto[92]	2004	57/W	Thymectomy	26 years after Thymectomy	Cyclosporine long view	PR hindsight ?
Yoshida[93]	2005	67/W	None	Concomitant	1. Thymectomy -> Radiotherapy 2. Corticosteroids + Cyclosporine 3. Tacrolimus + Corticosteroids	RP 8 years -> Relapse Persistent Disease 3M Relapse 5M -> PR 6M
Fukushima[94]	2006	33/M	Thymectomy -> Radiotherapy -> Ctp -> 2nd Surg/Ctp	1 week after 2nd Surgery /Chemotherapy	1. Corticosteroids + Tacrolimus 2. Cyclosporine long view	Persistent Disease PR hindsight 2 months
Jain[95]	2006	40/M	Thymectomy -> Rxpy	After Radiotherapy	Corticosteroids long view	CR with Cort hindsight ?
Van Der Marel[96]	2007	56/M	None	1 year before thymoma	1. Corticosteroids 1 year 2. Thymectomy	Persistent Disease 1Y CR hindsight 1,5 month
Zaucha[97]	2007	35/W	Ctp : 6ADCO -> 3Cis-Eto -> 6'Ifosfamide	After chemotherapy : 6'Ifosfamide	ACTH long view	CR hindsiht 9 months
Lucchi[98]	2007	43/M	None	Concomitant	Thymectomy + Radiotherapy	PR hindsight 5 years

Shiraishi[99]	2008	55/W	None	Concomitant	1. Corticosteroids + Cyclophosphamide 2. Thymectomy	Partial Remission Persistent Disease
Vohra[100] ***(SC)***	2008	58/M	None	Concomitant	Chemotherapy -> Thymectomy	CR hindsight ?
		45/W	None	Concomitant	1. Thymectomy 2. Androgens + Corticosteroids 3. Anti-Thymocytes globulins 4. Cyclosporine	PR-> Relapse Persitent Disease Persistent Disease PD follow-up ?
Ketata[101]	2009	59/W	Chemotherapy (4 cycles)	After the 4th cycle of chemotherapy	Corticosteroids 6 months	CR hindsight 7 months
Lin[102]	2009	46/W	None	Concomitant	Cort 14d -> Thymectomy -> Cort 1M	CR hindsight 3 years
Taniguchi[103]	2009	57/W	None	Concomitant	Thymectomy	PR hindsight 1 month
Jiang[104] ***(SC)***	2010	48/W	None	Concomitant	Thymectomy	CR hindsight 70 months
		54/M	None	Concomitant	Thymectomy	CR hindsight 68 months
		55/M	None	Concomitant	Thymectomy	CR hindsight 50 months
Khalid[105]	2010	35/W	None	Concomitant	Thymectomy	CR hindsight 3 years
Kuribayashi[106]	2010	79/W	None	Concomitant	Thymectomy	Persistent Disease 4M
Petakov[107]	2010	62/M	None	Concomitant	1. Thymectomy 2. Corticosteroids SV->Cort long view	Persistent Disease Rpse 2M-> CR 3,5 years
Chen[108]	2011	70/W	None	Concomitant	Thymectomy	Death in PR 16 months
De Castro[109]	2011	69/M	Thymectomy (CR)	3 years after thymectomy	Cyclosporine	CR hindsight 4 years
		59/W	Thymectomy ->Rxpy (CR)	18 months after Radiotherapy	Cyclosporine + Corticosteroids	Death in PD
Rosu[110]	2011	80/W	None	Concomitant	1. Thymectomy 2. Cyclosporine	CR 6 months -> Relapse CR hindsight?
Peña[111]	2012	70/M	Thymectomy	9 years after Thymectomy	Corticosteroids + Cyclosporine	Death in CR 3 months
Balikar[112]	2013	55/W	Thymectomy	Concomitant	Corticosteroids	PR hindsight 1 month
Briones[113]	2013	53/M	Thymetomy-> Rpse 1A : CAPPr	3rd Cycle CAPPr	Chemotherapy: Pacli-Carbo	PR hindsight ?
Kawano[114] ***(SC)***	2013	36/M	Thymectomy	After Thymectomy	Cyclosporine long view	CR hindsight 5 years
		46/W	Thymectomy	After Thymectomy	Cyclosporine long view	CR hindsight 5 years
		71/W	None	Concomitant	Corticoticosteroids long view	Death Thy/PRCA PR
Kojima[115]	2013	64/W	Thymectomy	4 years after Thymectomy	1. ATG + Cyclosporine	Persistent Disease

					2. Desafirox 7 months	CR hindsight 15 months
Rao[116]	2013	38/W	Thymectomy	2 months after Thymectomy	Corticosteroids	PR hindsight 1 year
Fallahi[117]	2014	54/W	Thymectomy	6 years after Thymectomy	Corticosteroids long view	CR hindsight 8 months
Gay[118]	2014	31/M	Thymectomy -> 2nd Surg 10Y-> Ctp	After chemotherapy	1. Cyclosporine + Corticosteroids -> ATG 2. Cyclosporine 3. Chemotherapy -> 3rd surgery	CR 3 months CR 9 months CR hindsight 6 months
Kobayashi[119]	2014	81/W	Thymectomy (Rpse 13A)	Concomitant with relapse's thymoma	2nd Surgery + Corticosteroids	PD hindsight ?
Marmont[120]	2014	55/W	None	3A before thymoma diagnostic	1. Antithymoglobulins 2. Thymectomy + Radiotherapy 3. Bone marrow allograft	CR -> Relapse CR -> Relapse CR follow-up 1 year
Fujiwara[121]	2015	44/W	Chemotherapy	During the Chemotherapy	1. Thymectomy 2. Corticosteroids	Persistent Disease PR hindsight 1 year
Tiwari[122]	2015	14M/	None	Concomitant	Thymectomy	CR hindsight 1,5 year
Antar[123]	2016	90/M	None	Concomitant	Rituximab	PR hindsight 9 months
Onuki[124]	2016	67/W	None	Concomitant	Cyclosporine + Thymectomy -> Rxpy	CR hindsight 1 year
Feinsilber[125]	2017	34/W	None	5years before Thymoma	1. Thymectomy+ Chemotherapy 2. 2nd Surgery + Radiotherapy	Persistent Disease PD follow-up ?
Isshiki[126]	2017	50/W	Thy-> Rpse 10Y: Cort + 2thSurg	3 years after the 2nd Thymic Surgery	Cyclosporine long view	CR hindsight 3 years
Korphaisarn[127]	2017	40/M	None	Concomitant	1. Thymectomy 2. Chloroquine + Corticoids->Clq + Aza	Persistent Disease CR hindsight 15 months
Li[128]	2017	47/M	Thymectomy -> Ctp(4)	After the 4th cycle of Chemotherapy	Cyclosporine+Corticosteroids->Ctp (4')	Death Thy/PRCA CR 2Y
Ferreira[129]	2018	73/M	None	Concomitant	Thymectomy	CR hindsight 1 year
Moriyama[130] ***(SC)***	2018	46/W	Cort -> Thymectomy -> Rxpy	3 months after Thymectomy	Corticosteroids + Cyclosporine	Death in CR 147 months
		71/M	None	60 months before Thymoma	Thymectomy	Death in PD 70 months
		45/W	Cort -> Thymectomy -> Rxpy	53 months after Thymectomy	Cyclosporine	Death in CR 22 months
		57/M	Thymectomy	101 months after Thymectomy	Corticosteroids + Cyclosporine	PD hindsight 39 months
		55/W	Thymectomy -> Rxpy	75 months after thymectomy	Cyclosporine	Death in PD 29 months
		51/M	Ctp-> Thymectomy -> Rxpy	1 month after thymectomy	Cyclosporine	Death in PD 103 months

		80/M	None	1 month before Thymoma	Corticoids-> Thymectomy	PD hindsight 87 months
		64/M	Cort-> Thymectomy -> Rxpy	60 months after thymectomy	Cyclosporine long view	CR CSP-> 13 months
Simkins[131]	2018	61/W	2 Cycles Ctp (4) -> Thymectomy	2 months after Thymectomy	1. Cyclosporine + Corticoids + ATG 2. Bone marrow allograft	PD 10 months PR hindsight 12 months
Tabata[132]	2018	40/W	Thy->ADOC (4)+ Cort + Tacro -> TS1(4)	After chemotherapy : TS1	Cyclosporine long view	RP hindsight 3 months
Tavakol[133]	2018	57/M	Thymectomy	6 years after thymectomy	1. Corticosteroids 2. Cyclosporine long view	Persistent Disease CR with CSP hindsight 4Y
Simkins[134]	2018	61/W	CAPP->Thymectomy	After Thymectomy	1. Corticosteroids + EPO + Cyclosporine 2. Anti-Thymocytes globulins 3. Bone marrow allograft	Persistent Disease PR 9M -> Relapse PR hindsight 1 year
Lo Iacono[135]	2019	62/W	Rxpy, Ctp, thymectomy	After thymectomy	1. Corticosteroids 2. Immunoglobulins 3. Plasmapherese + Corticosteroids	Persistent Disease Persistent Disease CR hindsight 6 months
Xiangli[136]	2019	61/M	None	Concomitant	1. Thymectomy + Radiotherapy 2. Corticosteroids – Csp – EPO	Persistent Disease 1M Complete Remission

List of Abbreviations:

ACTH, adrenocorticotropic hormone; ADOC, doxorubicine cisplatin vincristine cyclophosphamide; ALG, anti-lymphocyte globulins; And, androgens; ATG, anti-thymocyte globulins; Aza, azathioprine; Surg, surgery; Clq, chloroquine; Cort, corticoticosteroids; CAP, cisplatin doxorubicin cyclophosphamide; CPA, cyclophosphamide; CSP, cyclosporin; Ctp(X), chemotherapy (number of cycles); D, days; diag, diagnosis; EPO, erythropoietin; 6MP, mercaptopurine; M, male; W, women; GRC, red blood cells transfusion; Ig, Immunoglobulins; IST, immunosuppresants; IV, intraveinous; LV, long view; M, months; BM, Bone marrow; PRCA, pure red cell aplasia; CR, complete remission; Rpse, relapse; PR, partial remission; Rxpy, radiotherapy; Spl, splenectomy; Tacro, tacrolimus; Thy, thymectomy; TS 1, Titanium silicate; Y, year.

* The references can be found below (see page 15)

Table 3: PRCA responses in function of the treatment applied

Therapeutic sequence	CR	PR	PD
Anti-tumor treatment:			
- **Thymectomy**	**23**	**6**	**50**
- **Thymectomy + Chemotherapy**	**2**	**-**	**1**
- **Thymectomy + Radiotherapy**	**4**	**1**	**4**
- **Thymectomy + Chemotherapy + Radiotherapy**	**-**	**-**	**1**
- **Chemotherapy**	**-**	**1**	**3**
- **Radiotherapy**	**-**	**-**	**1**
- **Chemotherapy + Radiotherapy**	**-**	**-**	**1**
- **Total**	**29**	**8**	**61**
Treatments acting on the immune system:			
- **Corticosteroids**	25	5	31
- **Cyclosporin**	23	3	5
- **Cyclophosphamide**	2	-	2
- **Azathioprine**	1	-	2
- **Others IST unspecified**	6	-	2
- **Other monotherapy***	8	5	14
- **Corticoids + Cyclophosphamide**	9	1	7
- **Corticoids + Cyclosporin**	3	-	4
- **Others combinations**	4	4	15
- **Total**	81	18	82
Combination of anti-tumor treatment and treatments acting on the immune system:			
- **Thymectomy + Corticoids**	6	4	2
- **Thymectomy + Combination IST**	3	1	1
- **Thymectomy + Corticoids + Cyclosporin**	1	-	-
- **Chemotherapy + Combination IST**	2	-	2
- **Chemotherapy + Radiotherapy + Corticoids**	-	-	1
- **Radiotherapy + Combination IST**	1	4	1
- **Total**	13	9	7

Numbers are presenting the number of patients in each category

*adrenocorticotropic hormone; androgens; rituximab; splenectomy; anti-thymocytes globulins; immunoglobulins; bone marrow allograft; plasmapherese.

Table 4: PRCA rescue therapy and responses in case of PRCA persistence post-thymectomy

2nd line (N=44)*		3rd line (N=17)		More than 3 lines (N=11)	
Chemotherapy	1 PD	Allograft	1 CR 1 PR	Corticoids	2 CR 1 PD
Corticosteroids	7 CR 8 PD	Corticosteroids	2 CR 1 PD	Cyclosporine	2 CR 1PD
Cyclosporin	3 CR 2 PR	Cyclosporin	3 CR	IgIV	1 PR
CPA	2 PD	IgIV	1 PD	Others IST	1 CR
Azathioprine	1 CR	ATG	1 PD	Combinations	2PD
Androgens	1 CR 2 PD	Androgens	1 PD	ACTH	1CR
Others IST	3 CR	Splenectomy	1 CR 1PD		
Combinations	6 CR 1PR 7PD	Combinations	2 CR 2PD		

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