ORIGINAL ARTICLE

Thymic Epithelial Tumor-Associated Cytopenia: A 10-Year Observational Study in France

Claire Rivoisy, MD,[a] Benjamin Besse, MD,[b] Nicolas Girard, PhD,[c] Bertrand Lioger, MD,[d] Jean-Francois Viallard, PhD,[e] Jean-Christophe Lega, MD,[f,g] Patricia Rullier, MD,[h] Antoinette Perlat, MD,[i] Delphine Lerouge, MD,[j] Christelle Clement-Duchene, MD,[k,l] Mikael Ebbo, MD,[m] Annick Bosseray, MD,[n] Bertrand Godeau, PhD,[o] Olivier Lambotte, MD, PhD[a,p,q,r,*]

[a]*Department of Internal Medicine, Bicêtre Hospital, Le Kremlin Bicêtre, France*
[b]*Department of Cancer Medicine, Gustave Roussy Institute, Villejuif, France Paris-Sud University, Paris, France*
[c]*Department of Respiratory Medicine, Louis Pradel Hospital, Hospices Civils de Lyon, Lyon, France*
[d]*Department of Internal Medicine, University Medical Center Tours, Tours, France*
[e]*Internal Medicine Department, Bordeaux University Medical Center, Pessac, France*
[f]*UMR, Unite Mixte de Recherche 5558, Department of Internal and Vascular Medicine, University Medical Center Lyon Sud, Claude Bernard University Lyon 1, France*
[g]*Biometry and Evolutionary Biology Laboratory, Centre National de la Recherche Scientifique, Claude Bernard University Lyon 1, France*
[h]*Department of Internal Medicine, University Medical Center Montpellier, Montpellier, France*
[i]*Department of Internal Medicine, University Medical Center Rennes, Rennes, France*
[j]*Deparment of Pneumology and Thoracic Oncology, University Medical Center Caen, France*
[k]*Chest Department, University Medical Center Nancy, Nancy, France*
[l]*Research Team EA, Equipe Avenir 7298, INGRES, Lorraine University, Lorraine, France*
[m]*Department of Internal Medicine, La Conception Hospital, University Medical Center Marseille, Aix-Marseille University, Marseille, France*
[n]*Department of Internal Medicine, University Medical Center Grenoble, Grenoble, France*
[o]*Department of Internal Medicine, National Reference Centre for Autoimmune Cytopenia in Adults, Henri-Mondor University Hospital, University Medical Center Paris, Paris-Est Créteil University, Créteil, France*
[p]*Paris Sud University, UMR, Unite Mixte de Recherche 1184, France*
[q]*CEA, DSV/iMETI, Division of Immuno-Virology, Infectious Disease Models and Innovative Therapies, Le Kremlin Bicêtre, France*
[r]*Inserm, U1184, Center for Immunology of Viral Infections and Autoimmune Diseases, Le Kremlin Bicêtre, France*

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ABSTRACT

Introduction: Thymic epithelial tumor (TET)-associated cytopenia is rare but difficult to treat.

Methods: We performed a multicenter, retrospective study of TET and associated forms of cytopenia in France. Cases were collected by the French National Reference Center for Autoimmune Cytopenia and the French National Thymic Malignancy Interest Group (Réseau Tumeurs Thymiques et Cancer) and through a call for cases by the French Society of Internal Medicine.

Results: Thirty-six cases were recorded between 2002 and 2014 and followed up for a median of 38 months (interquartile range, 23–106 months). Thirty-two patients underwent surgery for TET, and 14 of the latter were in complete remission at last follow-up. Cytopenia can occur before, simultaneously, or after diagnosis of TET. The most common types of cytopenia were pure red cell aplasia (in 30% of cases) and Good syndrome (GS) (also in 30% of cases). Eleven patients displayed two or more episodes of cytopenia. Eighteen patients received steroids as their first-line treatment, leading to a complete response in nine. Other first-line treatments (cyclosporine and rituximab) were less effective but should be considered as treatment options. Infections developed in 84% of the patients with GS; this did not appear to be related to the presence or

*Corresponding author.

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Address for correspondence: Professor Olivier Lambotte, MD, PhD, Service de Médecine Interne, CHU Bicêtre, 78 rue du Général Leclerc, F-94275 Le Kremlin Bicêtre Cedex, France. E-mail: olivier.lambotte@bct.aphp.fr

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absence of immunosuppressive treatment or chemotherapy. Eight patients died during the follow-up period (two died of cytopenia and five of infections).

Conclusions: The optimal treatment for TET-associated cytopenia has not been clearly defined and the outcome does not appear to be correlated with TET progression. For GS, prophylactic immunoglobulin replacement therapy and prophylactic antibiotic therapy can be recommended.

Keywords: Thymic epithelial tumor; Pure red cell aplasia; Good syndrome; Infectious complications

Introduction

Thymic epithelial tumors (TETs), including both thymoma and thymic carcinoma, are rare: the overall incidence in the United States is 0.15 per 100,000 person-years. These tumors can be classified according to the extent of the disease (e.g., using the Masaoka-Koga staging system, as modified in 1994) and/or the histologic findings (e.g., using the World Health Organization local histologic classification of thymic tumors, as updated in 2004). Thymic epithelial tumors are frequently associated with parathymic diseases (including autoimmune manifestations); myasthenia gravis is the most frequent condition and affects between 30% and 50% of patients with TET.[1]

Thymic epithelial tumor–associated cytopenia has also been reported (it was first described in the 1980s) but is far less common than myasthenia gravis.[2] Pure red cell aplasia (PRCA) is defined as severe, normochromic, normocytic anemia associated with reticulocytopenia and the absence of erythroblasts in otherwise normal bone marrow[3]; it is reportedly the second most frequent autoimmune disease in patients with TET. A Japanese series described the diagnosis of 41 cases of PRCA over a 16-year period.[4] Other types of cytopenia have been described, albeit usually as case reports; they include immune thrombocytopenia,[5] autoimmune agranulocytosis,[6] autoimmune hemolytic anemia,[7] and Good syndrome (GS).[1] The latter is a puzzling entity observed in 5% of patients with TET[1]; it features a combination of B lymphopenia, variable CD8 and CD4 T-cell counts, hypogammaglobulinemia, and susceptibility to infections. The mechanisms underlying GS have not been determined. Other cases of cytopenia in patients with TET may be variously related to pernicious anemia (also known as Biermer anemia) and hypothyroidism.

The treatment of the rare, autoimmune forms of cytopenia is not as well codified as that of GS. Similarly, long-term outcomes in TET-associated, autoimmune forms of cytopenia have not been extensively described. We therefore decided to collect data on French cases of TET-associated cytopenia over a 10-year period and to describe the patients' characteristics, treatments, and outcomes.

Methods

Cases were identified in three settings: those diagnosed at the French National Reference Center for Autoimmune Cytopenia, those recorded after a national call from the French Society of Internal Medicine, and those reviewed since January 2012 in the tumor board by the French National Thymic Malignancy Interest Group (RYTHMIC [Réseau Tumeurs Thymiques et Cancer]). Data concerning TET (date of diagnosis, histologic characteristics, treatments, and outcome) and autoimmune cytopenia (date of diagnosis, type, clinical manifestations, and outcome) were collected retrospectively.

The date of TET diagnosis was considered to be the date of histologic confirmation or (if biopsy or surgery was not performed) the date on which the thymic tumor was discovered. Thymic epithelial tumors were classified according to both the modified Masaoka-Koga staging system and the 2004 World Health Organization classification.[1]

Members of the RYTHMIC network performed a systematic, histopathological review of all cases included in the present analysis. The study was approved by the Internal Review Board of Gustave Roussy, and the authors observed strict accordance with the Helsinki Declaration guidelines.

For descriptive purposes, the study results are expressed as a median (interquartile range [IQR]) or a number (percentage). Continuous variables were compared using the Mann-Whitney test and categorical variables were compared using a chi-square test or Fisher's exact test.

Definitions

The response to TET treatment was defined in accordance with the RECIST criteria: a complete response (CR) corresponded to the disappearance of all target lesions; a partial response (PR) corresponded to at least a 30% decrease in the sum of the target lesions' diameters (relative to the value before treatment); progressive disease (PD) was defined as an increase in the sum of the target lesions' diameters of at least 20% (relative to the lowest value recorded for each individual patient during the study); and stable disease (SD) was defined as all cases not meeting the criteria for a CR, PR, or PD (relative to the lowest value recorded for each individual patient during the study and with at least 1 year between the first and last evaluation).[8]

Cases of autoimmune cytopenia (PRCA, immune thrombocytopenia, autoimmune hemolytic anemia, and

Table 1. Characteristics of the 36 Patients

Characteristics	Patients (N = 36)	
Median age at thymoma diagnosis (IQR), y	55.6 (45.5-66.4)	
Sex ratio, M/F	18:18	
Histologic diagnosis of TET	A	n = 1
	AB	n = 9
	B1	n = 4
	B2	n = 6
	B3	n = 1
	B1-B3	n = 1
	B2-B3	n = 5
	B3-C	n = 1
	C	n = 4
	NR	n = 4
Masaoka stage at thymoma diagnosis	I	n = 11
	II	n = 7
	III	n = 5
	IV	n = 8
	NR	n = 5
Additional thymoma treatment	Radiotherapy	n = 7
	Chemotherapy	n = 4
	Both	n = 8
Median interval between diagnoses of TET and first episode of cytopenia (IQR), d[a]	77 (-21.75 to 721.5)	
Thymoma status at cytopenia diagnosis	TET preceding cytopenia	n = 24
	Progressive disease	n = 7
	Stable disease	n = 7
	Complete response	n = 10
	Cytopenia concomitant	
	With TET diagnosis	n = 13
	Not still diagnosed	n = 5
Type of cytopenia	PRCA	n = 19
	GS	n = 19
	AA	n = 5
	ITP	n = 4
	AIHA	n = 2
	≥2 associated types of cytopenia	n = 11
Associated autoimmune manifestations	SLE	n = 4
	ANA	n = 13
	SS	n = 1
	Coombs	n = 2
	RA	n = 1
	MG	n = 12
	Oral lichen planus	n = 4
	Thyroiditis	n = 2
	Nervous system autoimmune manifestations	n = 3

[a]Interval is given as a positive number if the diagnosis of thymoma preceded the diagnosis of cytopenia and as a negative number if the diagnosis of cytopenia preceded the diagnosis of thymoma.
IQR, interquartile range; M, male; F, female; TET, thymic epithelial tumor; NR, not reported; PRCA, pure red cell aplasia; GS, Good syndrome; AA, acquired agranulocytosis; ITP, immune thrombocytopenia; AIHA, autoimmune hemolytic anemia; RA, rheumatoid arthritis; MG, symptomatic myasthenia gravis or a positive test for antibodies against the acetylcholine receptor; SLE, systemic lupus erythematosus; SS, Sjogren syndrome; Coombs, positive Coombs test in the absence of hemolytic anemia; ANA, positive test for antinuclear antibodies.

autoimmune agranulocytosis) and their response to treatments were defined in accordance with published consensus statements and definitions.[4,9–12]

Good syndrome is an adult-onset immunodeficiency defined by low or null B-cell counts in peripheral blood, hypogammaglobulinemia, and (in some cases) defects in cell-mediated immunity ($CD4^+$ T lymphopenia and an inverted $CD4^+/CD8^+$ T-cell ratio).[13,14]

Results

Incidence of TET-Associated Cytopenia

The incidence of TET-associated cytopenia could be estimated from the RYTHMIC database. From January 2012 to October 2014, 702 cases of TET were reviewed. Of these patients, 102 (14.5%) had autoimmune conditions and nine (1.3% of all patients) presented with cytopenia (i.e., with TET): two with autoimmune hemolytic anemia, one with immune thrombocytopenia, one with GS, and five with PRCA.

Characteristics of Patients with TET

Thanks to the efforts of the RYTHMIC network, the French National Reference Center for Autoimmune Cytopenia, and the French Society of Internal Medicine, 36 cases were retrospectively recorded: 18 involving men and 18 involving women, with a median age at TET diagnosis of 55.8 years (IQR = 45.5–66.4). The TET was localized (i.e., a Masaoka-Koga stage of I or II) in half the cases. Type A thymoma and thymic carcinoma were less frequent than type AB, B1, and B2 tumors. Interestingly, type B3 was usually combined with types B1 and B2. No one histologic form was predominant or appeared to be associated with a specific type of cytopenia. Only four patients (median age at diagnosis, 63 years; IQR = 55.7–67) had thymic carcinoma.

Thirty-two patients underwent surgery for TET. Complete resection was obtained in 22 patients. One patient refused surgery, and the tumor in three patients was not resectable. Fifteen patients underwent mediastinal radiotherapy as their first-line treatment, whereas eight patients underwent cytotoxic chemotherapy Twenty-eight patients displayed a CR after the first course of treatment. Thirteen patients displayed a PR or PD and thus underwent second-line treatment (chemotherapy or repeat surgery). At last follow-up, 14 patients displayed a CR, one patient displayed a PR, three patients had PD, 10 patients had SD, and eight patients had metastatic disease. Eight patients died (six with a CR, one with PD, and one with SD), but none of the deaths were related to TET progression.

Characteristics of Patients with Autoimmune Cytopenia

Forty-two cases of cytopenia were recorded. Their characteristics are summarized in Tables 1, 2, and 3. Cytopenia was variously diagnosed concomitantly with

TET: within 60 days in 13 cases; before TET in five cases (median interval, 147 days; IQR = 74–664), or after TET in 24 cases (median interval, 852 days; IQR = 315–1484). At the time when cytopenia was diagnosed, eight of these patients had stable TET disease with metastasis, 10 were in complete remission, and seven had PD.

PRCA and GS were the most frequently observed types of cytopenia (n = 19 for each). Twenty-five patients presented with a single type of cytopenia: 11 with GS, 11 with PRCA, two with autoimmune agranulocytosis, and one with immune thrombocytopenia. Several types of cytopenia developed in 11 patients: cytopenia was diagnosed concomitantly in six cases and with a median interval between diagnoses of 2013 days (IQR = 360–2248) in the other five cases.

Clinical autoimmune disease was observed in 23 patients (mainly myasthenia gravis [n = 12] and lupus [n = 4]). Biological markers of autoimmunity (such as antinuclear antibodies) were observed in 13 patients.

Characteristics of Patients with TET-Associated Cytopenia but Not GS

PRCA, autoimmune hemolytic anemia, autoimmune agranulocytosis, or immune thrombocytopenia was diagnosed in 17 patients (Tables 2 and 4).

Eleven patients had isolated PRCA. The median hemoglobin level at diagnosis was 7 g/dL (IQR = 5.45–8.2) and the median reticulocyte count was 7000 per mm^3 (IQR = 4200–11,640). The median interval between the respective diagnoses of TET and PRCA was 170 days (IQR = −14 to 580), with PRCA diagnosed from 3 years before TET diagnosis to 7 years after TET diagnosis. All patients required blood transfusion. Seven patients received first-line treatment with steroids. Other treatments were rituximab (n = 1) and cyclosporine (n = 3). PRCA recurred in three patients and was treated with various medications (including danazol, immunoglobulins administered intravenously, alemtuzumab, and antilymphocyte serum [see Table 4]).

Other types of cytopenia were diagnosed in six patients: immune thrombocytopenia (n = 1), autoimmune agranulocytosis (n = 2), and PRCA diagnosed at the same time as another type of autoimmune cytopenia (n = 3).

Strikingly, eight patients without GS had infectious complications; these included not only bacterial infections but also opportunistic infections (e.g., cytomegalovirus infection, pneumocystis pneumonia, and reactivation of herpes zoster). It is noteworthy that eight of the patients presenting with TET-associated cytopenia were also being treated for TET at the same time (radiotherapy [n = 2], chemotherapy [n = 5], and both [n = 1]; see Table 2).

We compared the outcome of cytopenia as a function of the thymoma's response. Of the nine patients with a CR for TET, three experienced at least one relapse of cytopenia. One patient died from infectious complications. Of the eight patients with progressive TET, four experienced a relapse of cytopenia. Two patients with progressive TET died (one of infectious complications and the other of thrombocytopenia). These two groups of patients (CR versus progressive TET) did not differ significantly in terms of the relapse rate ($p = 0.64$) or the mortality rate ($p = 0.57$). Hence, the outcome of cytopenia did not appear to be associated with the TET response.

Characteristics of the Patients with GS

Nineteen patients (10 men and nine women; median age, 62.3 years; IQR = 53.1–68.75) had GS (see Table 3). Eleven patients had isolated GS, and the remaining eight had concomitant autoimmune cytopenia. The median follow-up time was 26 months (IQR = 20.5–49). All patients had hypogammaglobulinemia. The median immunoglobulin level was 2.75 g/L (IQR = 1.625–4.675). Lymphocyte counts and typing data were available for 16 patients: all had a low B-lymphocyte count and 11 patients had no circulating B lymphocytes. Twelve patients had a CD4/CD8 T-cell ratio less than 1.

Infectious disease developed in all but three of these patients. Nineteen episodes of pneumonia (mainly involving the bacteria *Streptococcus pneumonia, Haemophilus influenzae*, and *Pseudomonas aeruginosa*), three episodes of sinusitis, and two severe soft-tissue infections were reported. Opportunistic infections were diagnosed in eight patients (cytomegalovirus in four patients, herpes zoster in four, and atypical disseminated mycobacterial infections in two). Fungal infections were also observed (invasive aspergillosis in three patients and recurrent mucosal candidiasis in three). Of the eight patients with associated autoimmune cytopenia, six received immunosuppressive treatment and two (with autoimmune agranulocytosis) were treated with granulocyte colony-stimulating factor.

Only 16 patients received prophylactic immunoglobulin therapy (administered intravenously or subcutaneously), and 10 patients received prophylactic antibiotic therapy (cotrimoxazole [n = 6], amoxicillin [n = 2], azithromycin [n = 2], inhaled pentamidine [n = 3], and atovaquone [n = 1]).

When we compared the two groups of patients with GS (those with cytopenia and those without cytopenia), there was no difference in the outcome and the number of infections even though one group was receiving immunosuppressive treatment for cytopenia (see Table 3). Likewise, there was no difference in the incidence of bacterial infections ($p = 0.52$) or opportunistic infections ($p = 0.68$) according to whether the patients with GS received chemotherapy for TET.

Of the five patients who died as a result of infectious complications, four had GS. One had autoimmune

Table 2. TET-Associated Autoimmune Cytopenia

Patient Characteristics	PRCA	ITP	AA	Multiple Episodes of Autoimmune Cytopenia (PRCA + AIHA, PRCA + ITP, PRCA + ITP + AA)
No. patients	11	1	2	3
Gender, M/F	4:7	0:1	0:2	3:0
Median age (IQR), y	57.4 (45.9-64)	27.1	59.25 (48-70.4)	46 (37-53.1)
Median time between TET and cytopenia diagnosis (IQR), d	170 (-14 to 580)	-2	2082 (1259-2905)	-63 (-549 to 43)
Status of thymoma at diagnosis				
Progressive disease	3			2
Stable disease	1		1	
Complete response	3		1	
Partial response				
Diagnosed very recently	3	1		
Not diagnosed	1			1
Concomittant thymoma treatment				
Chemotherapy	3			2
Radiotherapy	1			1
Both	1			
None	6	1	2	
Initial efficacy of cytopenia treatment				
Complete remission	7			1
Partial remission	3		2	2
Failure	1	1		
Relapse of the cytopenia				
Yes	3	1	1	2
No	8		1	1
Intercurrent infections				
Yes	4		2	2
No	7	1		1
Type	VZV reactivation, bacterial pneumonia, facial cellulitis, CMV reactivation, pneumocystis pneumonia		Septic shock, pneumonia	Necrotizing angina, pancolitis
Median time of follow-up (IQR), mo	23 (16-29)	1	11 (9.5-12.5)	34 (27-37.5)
Global outcome				
Death (due to cytopenia)	2 (1)	1 (1)		
Alive	9		2	3
Thymoma outcome				
Progressive disease	2			
Stable disease	2	1	1	1
Complete response	7		1	1
Partial response				1
Cytopenia outcome				
Complete remission	6			1
Partial remission	3		2	2
Active disease	2	1		

TET, thymic epithelial tumor; PRCA, pure red cell aplasia; ITP, immune thrombocytopenic purpura; AA, autoimmune agranulocytosis; AIHA, autoimmune hemolytic anemia; M, male; F, female; IQR, interquartile range, VZV, varicella zoster virus; CMV, cytomegalovirus.

agranulocytosis, another underwent intensive immunosuppressive treatment with alemtuzumab for relapsing PRCA and chemotherapy for progressing TET, one patient received steroids for PRCA, and the remaining two patients did not receive immunosuppressive treatment.

Immunosuppressive Treatments

With regard to immunosuppressive treatments (Table 4), steroids alone were prescribed for 19 patients, and they led to a CR in eight patients with PRCA and one with autoimmune hemolytic anemia. In the

Table 3. Good Syndrome

Patient Characteristics	Isolated Good Syndrome	Good Syndrome Associated with Autoimmune Cytopenia	*p* Value
No. patients	11	8	
Gender, M/F	6:5	4:4	
Median age (IQR), y	62.4 (57.3–56.3)	57.5 (51.7–74.4)	0.9
Type of cytopenia			
Pure red cell aplasia		5	
Other		3	
Concomitant cytopenia treatment			
Yes		5	
No		3	
Status of thymoma at diagnosis			
Progressive disease	1	1	
Stable disease	3	3	
Complete response	7	4	
Concomittant thymoma treatment			
Chemotherapy		1	
Radiotherapy		1	
Both	2	1	
None	9	5	
Median gammaglobulines level (IQR), g/L	2.7 (1.4–3.9)	4 (1.8–4.7)	0.4
Intercurrent infections			
Yes	10	6	0.5
No	1	2	
Type	Bacterial pneumonia, sinusitis, mucosal candidiasis, CMV and VZV infections, pulmonary aspergillosis, meningococcal bacteremia, pneumococcal endocarditis, chronic diarrhea, cutaneous abscess, *Campylobacter* bacteremia	Bacterial pneumonia, chronic diarrhea, VZV and CMV infections, septic shock, cutaneous abscess, *Mycobacterium chelonae* and *Mycobacterium kansasii* infections, pulmonary aspergillosis, mucosal candidiasis, *Citrobacter freundii* sepsis	
Antibioprophylaxis	5	5	0.6
Immunoglobulines replacement	11	5	0.2
Median time of follow-up (IQR), mo	25 (17.5–47)	29 (22.5–58)	0.6
Global outcome			
Death (due to cytopenia)	4 (3)	1 (1)	0.3
Alive	7	7	
Thymoma outcome			
Progressive disease	1	1	
Stable disease	3	3	
Complete response	7	4	

seven patients suffering from PRCA, cyclosporine alone led to a CR in one case. Steroids were combined with other drugs in five patients: with cyclosporine in two cases (with one CR), rituximab in two cases (with two CRs), and cyclophosphamide in a patient with autoimmune hemolytic anemia (leading to a CR). Rituximab was administered to six patients and resulted in a CR in two cases (a patient with PRCA and a patient with immune thrombocytopenia). Immunoglobulins, cyclophosphamide, and mycophenolate mofetil alone were ineffective.

In the context of autoimmune neutropenia, treatment with granulocyte colony-stimulating factor alone resulted in a CR in two patients. Other treatments for autoimmune agranulocytosis led only to a PR. Steroids did not lead to a CR in any of the patients suffering from immune thrombocytopenia. One patient displayed a CR after treatment with rituximab. Another patient displayed a PR after steroid treatment, and hydroxychloroquine was then added to maintain the response. One patient died despite the perioperative administration of eltrombopag, steroids, and immunoglobulins. The last patient displayed a PR despite the successive administrative of several treatments (immunoglobulins administered intravenously, danatrol, and cyclosporine).

Table 4. Treatments and Responses

	Pure Red Cell Aplasia (n = 19[a])		Autoimmune Neutropenia (n = 5[a])		Autoimmune Hemolytic Anemia (n = 2)		Immune Thrombocytopenia (n = 4[a])	
Treatment	No. patients	Treatment response (n)	No. patients	Treatment response	No. patients	Treatment response	No. patients	Treatment response
Corticosteroids alone	13	CR (8) PR (3) PD (2)	2	PR	1	CR	3	PD (2) PR (1)
Cyclosporine alone	7	PR (3) CR (1) Intolerance (2) PD (1)						
Cyclosporine + corticosteroids	2	PR (1) CR (1)						
Rituximab	4	CR (1) PR (1) PD (2)	1	PR				
Cyclophosphamide	1	PD			1	CR		
Alemtuzumab	1	CR						
Mycofenolate mofetil	2	PD						
G-CSF			2	CR				
Azathioprine + plasmatic exchange			1	PR				
Rituximab + Ig corticosteroids	1	CR					1	CR
Ig	4	PD					1	PD
Hydroxychloroquine							1	PR
Eltrombopag							1	PR
Antilymphocyte serum	1	PD						
Danazol	2	PD						

[a]A given patient may have received several different treatments.
CR, complete response; PR, partial response; PD, progressing disease; G-CSF, Granulocyte colony-stimulating factor; Ig, immmunoglobulin.

Outcomes

The median total follow-up time was 38 months (IQR = 23–106). Eight patients (22%) died during the follow-up period. One death was due to glioblastoma, one was due to uncontrolled immune thrombocytopenia, one was due to central thrombocytopenia from an unknown cause, and five were due to infectious complications. None of the deaths were related to TET progression.

Discussion

To the best of our knowledge, the present study is the first to have systematically recorded the various types of cytopenia associated with TET.

As described earlier, GS and PRCA were the most common types of TET-associated cytopenia. We observed only five cases of autoimmune agranulocytosis, four cases of immune thrombocytopenia, and two cases of autoimmune hemolytic anemia. These data are concordant with the results of a previous single-center retrospective study.[15] Interestingly, the combination of GS and autoimmune cytopenia was frequently observed (n = 8 [23%]) in our study. In a literature review of 152 patients with GS, associated autoimmune cytopenia was observed in 23.6% of cases.[16] Thirty percent of the affected patients had several forms of cytopenia.

After performing a large cohort study, Hirokawa et al. recommended cyclosporine as the first-line treatment for PRCA.[4] In our study, cyclosporine led to a CR in only one of the seven treated patients. Furthermore, two of the seven treated patients experienced side effects (arterial hypertension, renal insufficiency, and intolerance). In the present study, treatment of 13 patients with steroids led to eight CRs. Another striking feature was rituximab's potential ability to avoid the need for long-term administration of immunosuppressive drugs for this indication. Of the four patients treated with rituximab, two showed a CR, one showed a PR, and the remaining patient failed to respond. Hence, rituximab might be a valuable option in fragile patients. Moreover, some TETs may express CD20, which would be another reason for using rituximab.[17] In contrast, neither immunoglobulin infusion nor mycophenolate mofetil led to a satisfactory outcome. Hence, steroids and cyclosporine remain the primary treatments for TET-associated PRCA.

The present study is also one of the largest to have described patients with GS. Our findings emphasized the severity of this condition because all four patients with fatal infections had GS. The association of autoimmune cytopenia with immunosuppressive therapy and GS might have increased the incidence of infectious complications in patients with GS. Interestingly, the proportion of patients with GS and opportunistic infections and severe bacterial infections was the same as that of those taking immunosuppressive drugs (six of eight) and those not taking immunosuppressive drugs (nine of 10). This finding emphasizes the truly profound immunodeficiency in GS. Hence, with close monitoring and follow-up, standard treatments for autoimmune cytopenia can be used in the context of GS. Conversely, infectious complications were less common in patients with autoimmune cytopenia but not GS (six of 16). Our results underline the importance of screening for immunological features of GS before initiating immunosuppressive treatments in a patient in whom autoimmune cytopenia has been diagnosed. Measurement of immunoglobulin titers, CD4 lymphocyte phenotyping, and B-cell counts are mandatory in this context.

Of the patients with GS, 16 (84%) received immunoglobulin replacement therapy. This might have reduced the mortality rate in our series (22%), which was lower than those reported in various literature series (30% after 5 years in a large series published in 1993,[18] 46% in a recent literature review,[16] and 30% in a very recent study[19]). In our series, however, the four patients with GS who died (of severe lung infections) were receiving immunoglobulins but not prophylactic antibiotic therapy. The last patient to die presented with progressive, extensive TET, and metastases and thus required several courses of chemotherapy. He received alemtuzumab for progressing PRCA; this intense immunosuppression might explain the frequent infectious complications and, ultimately, death. These observations suggest that patients with GS probably require long-term, high-dose immunoglobulin replacement therapy to significantly reduce the rate of infectious complications. Strong immunosuppressants (such as alemtuzumab and antilymphocyte serum) should probably be avoided, and trimethoprim should probably be introduced.

The frequency of infectious complications in patients with progressing TET might have been increased by cytotoxic chemotherapy. Indeed, 12 patients received chemotherapy as a first-line treatment for TET or at the time of relapse or disease progression. Bacterial infections developed in three of these patients, and one died. From these data we infer that the chemotherapy used to treat extensive TET can be used in patients with GS and/or immune cytopenia but should be monitored very closely.

As reported in the literature, thymomectomy did not appear to effectively cure cytopenia or correct the immunosuppressed state in the patients studied here.[4,16]

In the present series, we observed a CR of cytopenia in 50% of patients and a PR in 34%; however, there does not appear to be a single accepted standard treatment in this context. Steroids were more effective than other immunosuppressive drugs in treating PRCA. Relapses of TET-associated cytopenia appear to be especially difficult to treat. This has already been reported (for cases of PRCA) by the Japanese collaborative group and also

seems to be true for our immune thrombocytopenia patients.[20]

The present study had several limitations. First, the study's retrospective design probably increased the proportion of missing data. Second, our data collection was not exhaustive because cases were reported spontaneously. In fact, the French National Reference Center for Autoimmune Cytopenia and the French Society of Internal Medicine do not maintain exhaustive national databases. The RYTHMIC network plans to record and analyze all cases of TET nationwide but was set up only in 2012. The RYTHMIC network has however provided an accurate estimate of the incidence of TET-associated immune cytopenia in France, with nine cases occurring among 702 patients with TET over a 3-year period. However, the incidence of PRCA is too low to provide a reliable estimate of the relative incidence of each syndrome with thymoma versus with thymic carcinoma versus in the general population.

In conclusion, we have reported on treatments and outcomes in a series of 36 cases of TET-associated cytopenia. Our findings suggest that with close monitoring (gammaglobulin levels, the lymphocyte phenotype, etc.) it is possible to use (1) chemotherapy to treat extensive TET and (2) immunosuppressive drugs to treat autoimmune cytopenia—even when GS is also present.

PRCA was the most frequently observed type of cytopenia; treatment with steroids and cyclosporine appears to be the most likely to achieve a CR. Rituximab could be used as a salvage treatment for this indication.

To determine the optimal treatments for autoimmune agranulocytosis, autoimmune hemolytic anemia, and immune thrombocytopenia, a cohort study is now required. Implementation of a national registry would be of value in this respect.

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References

1. Ruffini E, Venuta F. Management of thymic tumors: a European perspective. *J Thorac Dis*. 2014;6(suppl 2): S228–S237.
2. Degos L, Faille A, Housset M, et al. Syndrome of neutrophil agranulocytosis, hypogammaglobulinemia, and thymoma. *Blood*. 1982;60:968–972.
3. Dessypris EN, Lipton JM. Red cell aplasia. In: Greer JP, Foerster J, Lukens JN, Rodgers GM, Paraskevas F, Glader B, eds. *Wintrobe's Clinical Hematology*. Philadelphia, PA: Linpiccott Williams and Wilkins; 2004:142–147.
4. Hirokawa M, Sawada K, Fujishima N, et al. Long-term response and outcome following immunosuppressive therapy in thymoma-associated pure red cell aplasia: a nationwide cohort study in Japan by the PRCA collaborative study group. *Haematologica*. 2008;93:27–33.
5. Qin J, Liu L. Thymoma with idiopathic thrombocytopenic purpura: report of a case. *J Thorac Cardiovasc Surg*. 2005;129:453.
6. Jethava Y, Alamelu J, Rangarajan S, et al. Acquired agranulocytosis and factor XI deficiency in association with thymoma. *J Clin Oncol*. 2011;29:e604–e606.
7. De Keyzer K, Peeters P, Verhelst C, et al. Autoimmune haemolytic anaemia associated with a thymoma: case report and review of the literature. *Acta Clin Belg*. 2009;64:447–451.
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
9. Lechner K, Jäger U. How I treat autoimmune hemolytic anemias in adults. *Blood*. 2010;116:1831–1838.
10. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113:2386–2393.
11. Roumier M, Loustau V, Guillaud C, et al. Characteristics and outcome of warm autoimmune hemolytic anemia in adults: New insights based on a single-center experience with 60 patients. *Am J Hematol*. 2014;89:E150–E155.
12. Haddy TB, Rana SR, Castro O. Benign ethnic neutropenia: what is a normal absolute neutrophil count? *J Lab Clin Med*. 1999;133:15–22.
13. Al-Herz W, Bousfiha A, Casanova J-L, et al. Primary immunodeficiency diseases: an update on the classification from the International Union Of Immunological Societies Expert Committee for Primary Immunodeficiency. *Front Immunol*. 2014;5:162.
14. Tarr PE, Sneller MC, Mechanic LJ, et al. Infections in patients with immunodeficiency with thymoma (Good syndrome). Report of 5 cases and review of the literature. *Medicine (Baltimore)*. 2001;80:123–133.
15. Holbro A, Jauch A, Lardinois D, et al. High prevalence of infections and autoimmunity in patients with thymoma. *Hum Immunol*. 2012;73:287–290.
16. Kelesidis T, Yang O. Good's syndrome remains a mystery after 55 years: A systematic review of the scientific evidence. *Clin Immunol*. 2010;135:347–363.
17. Marx A, Ströbel P, Badve SS, et al. ITMIG consensus statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. *J Thorac Oncol*. 2014;9:596–611.
18. Hermaszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *Q J Med*. 1993;86:31–42.
19. Malphettes M, Gérard L, Galicier L, et al. Good Syndrome: An adult-onset immunodeficiency remarkable for its high incidence of invasive infections and autoimmune complications. *Clin Infect Dis*. 2015;61:e13–e19.
20. Hirokawa M, Sawada K, Fujishima N, et al. Long-term outcome of patients with acquired chronic pure red cell aplasia (PRCA) following immunosuppressive therapy: a final report of the nationwide cohort study in 2004/2006 by the Japan PRCA Collaborative Study Group. *Br J Haematol*. 2015;169:879–886.