**Long term follow-up of pediatric-onset Evans syndrome: broad immunopathological manifestations and high treatment burden**

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**ABSTRACT**

Pediatric-onset Evans syndrome (pES) is defined by both immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) before the age of 18 years. There have been no comprehensive long-term studies of this rare disease, which can be associated to various immunopathological manifestations (IM). We report outcomes of the 151 patients with pES and more than 5 years of follow-up from the nationwide French prospective OBS’CEREVANCE cohort. Median age at final follow-up was 18.5 years (range, 6.8–50.0 years) and the median follow-up period was 11.3 years (range, 5.1–38.0 years). At 10 years, ITP and AIHA were in sustained complete...
remission in 54.5% and 78.4% of patients, respectively. The frequency and number of clinical and biological IM increased with age: at the age of 20 years, 74% had at least one clinical IM (cIM). A wide range of cIM occurred, mainly lymphoproliferation, dermatological, gastrointestinal/hepatic and pneumological IM. The number of cIM was associated with a subsequent increase in the number of second-line treatments received (other than steroids and immunoglobulins; hazard ratio 1.4, 95% Confidence Interval: 1.15–1.60, P=0.0002, Cox proportional hazards method). Survival at 15 years after diagnosis was 84%. Death occurred at a median age of 18 years (range, 1.7–31.5 years), and the most frequent cause was infection. The number of second-line treatments and severe/recurrent infections were independently associated with mortality. In conclusion, long-term outcomes of pES showed remission of cytopenias but frequent IM linked to high second-line treatment burden. Mortality was associated to drugs and/or underlying immunodeficiencies, and adolescents-young adults are a high-risk subgroup.

Introduction

The presence of both immune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) defines Evans syndrome (ES). Pediatric-onset ES (pES) is a rare disease, and approximately ten new cases are diagnosed every year in France, which has a population of 66 million.1 Since its first description in 1951 by Robert Evans,2 our understanding of pES has been based on small retrospective cohorts with limited follow-up.3,7 In 2004, the French Rare Disease Center CEREVANCE set up the prospective national cohort OBS’CEREVANCE, which includes children with AIHA, chronic ITP persisting for more than 12 months (cITP), and pES.8

Preliminary reports from this cohort and previously published studies showed that pES is a chronic disease with a high rate of relapse for both types of cytopenias.1,3,4,7,9 Mortality rates across studies have ranged from 7–36%.1,3,7 In addition to cytopenias, immunopathological manifestations (IM) such as autoimmune/autoinflammatory organ diseases, lymphoproliferation, and hypogammaglobulinemia have been reported in 70–80% of patients with pES.4,5,8,10 In an undetermined number of cases, pES is thought to be “secondary” and caused by an underlying disease, classically systemic lupus erythematosus (SLE) or autoimmune lymphoproliferative syndrome (ALPS).1,11,12 Recently, genetic analyses found a heterogeneous genetic background in up to 65% of a subset of 80 patients from the OBS’CEREVANCE cohort. These patients carried variants in genes that are linked to primary immunodeficiencies (PID) or involved in immune responses.13

Overall, outcomes and the long-term course of pES are poorly understood. There have been no comprehensive longitudinal studies including both cytopenia and IM. In addition, the transition to adulthood is often particularly challenging for patients with chronic pediatric diseases.14 Adolescents–young adults (AYA) outcomes have not been investigated in patients with pES, and whether the disease improves with age is unknown. In a clinical setting, the possibility to identify high-risk patients would be extremely helpful in the management of this complex disease. Here, we describe the long-term course of hematological IM and treatments received throughout childhood into adulthood in patients with pES from the OBS’CEREVANCE cohort. We aimed to identify clinically relevant factors associated to the occurrence of IM, the number of second-line treatments received and mortality. Particularly, we investigated the impact of the number second-line treatment received and splenectomy on mortality.

Methods

OBS’CEREVANCE prospective national cohort

Inclusion and exclusion criteria are shown in the Online Supplementary Table S1.1,4,15 Data collected have been previously detailed.1,8 Patients were included if <18 years old at first cytopenia diagnosis. The coordinating center gathered and analyzed all data from the medical team in charge in real time, enabling prospective follow-up even after the pediatric-to-adult transition. The CEREVANCE group recommends scheduling clinical and biological follow-up at least every 6-12 months. Some patients underwent genetic analyses, as previously described.15 Written informed consent was obtained from parents and eligible patients. The cohort study was approved by the Institutional Ethics Committee (CPPRB-A; Bordeaux, France) and the database was registered with the national data protection authority (CNIL, 1396823V0).

Patient selection

Patients with pES, defined as the simultaneous (within 1 month) or sequential association of ITP and AIHA, were included if at least 5 years of follow-up data were available after the first cytopenia diagnosis. In order to provide a complete mortality report, all patients, including those with less than 5 years of follow-up data, were included in the survival analyses. The data were extracted on 21 June 2019.

Definitions

Initial cytopenia refers to the onset of ITP or AIHA (whichever occurred first) and does not take autoimmune neutropenia (AIN) into account. The IM categories were separated in clinical (cIM) and biological (bIM). pES was defined as secondary if a diagnosis of SLE or PID was made during the follow-up period. SLE diagnosis was made according to the Systemic Lupus International Collaborating Clinics Classification criteria (SLICC).16 ALPS diagnosis was based on international criteria.17 Second-line treatments were all immunomodulatory or immunosuppressive treatments, including splenectomy but excluding steroids and therapeutic intravenous immunoglobulins (IVIG). Sustained complete remission (CR) was defined as remission persisting until final follow-up, regardless of ongoing treatments.

For analyses by age, patients were assessed annually from birth (for IM and treatments) or from cytopenia onset (for AIHA and ITP), until final follow-up. Occasional treatments (e.g., splenectomy and rituximab) were considered as ongoing if these occurred during the previous year. Further details are stated in the Online Supplementary Table S1.

Statistical analyses

Continuous and categorical variables were compared using Wilcoxon–Mann–Whitney non-parametric test and Fisher’s exact test, respectively. Correlations were tested using the Pearson cor-
relation coefficient. Survival and cumulative incidence estimates were based on the Kaplan–Meier method and compared using log-rank test. Patients of OBS’CEREVERANCE cohort with isolated cITP or AIHA were used for comparison in survival analyses (unpublished data). The Cox proportional hazards method was used to analyze factors associated with time-dependent variables (i.e., time to CR, AIN, cIM, and second-line treatment, as well as survival). The potential cumulative and/or time-dependent nature of variables was taken in account. Proportionality of hazard was assessed for each variable. Logistic regression was used to analyze factors associated with severe or recurrent infections. Variables that were statistically significant in the univariate analyses were included in the multivariate analyses. We investigated associations with the following characteristics and events: sex, consanguinity, cIM/cancer in a first-degree relative, age at first and second cytopenia, sequence of cytopenia, AIN, hypogammaglobulinemia, time to ITP/AIHA CR, severe/recurrent infections, number of cIM, number of second-line treatments. The 95% Confidence Intervals (CI) for hazard ratios (HR) and odds ratios (OR) were not adjusted for multiple testing and should not be used to infer definitive conclusions.

Results

Population

Of the 216 patients with pES, 151 were included in this study (Online Supplementary Figure S1). They were followed from 25 different centers. Patient characteristics are shown in Table 1. The median (min–max) follow-up time was 13.8 years (range, 5.1–38.0 years). Median age at final follow-up was 18.5 years (range, 6.8–50.0 years). In 20 cases (15%), follow-up was discontinued because the patient was considered cured (n=11) or lost to follow-up (n=9). Median age at loss to follow-up was 18.4 years (range, 6.8–25.1 years).

Hematological outcomes

AIN developed in 43 patients (28.5%). It was diagnosed within 1 month before or after first cytopenia onset in 23 of 43 cases (53.5%), more than 1 month before in two cases (4.7%), and more than 1 month after in 18 cases (41.9%; maximal delay, 12.4 years). In all cases, the diagnosis was made before the age of 15 years (median age, 6.8 years; range, 0.6–16.2 years). ITP and AIHA flare rates at 5 years of follow-up were calculated for the 61 alive patients who did not receive a second-line treatment during this period. Forty-eight patients (79%) had experienced an ITP flare and seven (11%) an AIHA flare.

The proportion of patients achieving sustained CR for ITP and AIHA steadily increased after cytopenia onset (Figure 1A). At 5 and 10 years, ITP was in sustained CR in 40.5% and 62.3% of patients (P=0.02) and AIHA was in sustained CR in 54.5% and 74.1% of patients (P=0.001), respectively. Sustained CR was achieved earlier for AIHA than ITP (median time to CR, 4.0 years vs. 7.0 years; P=0.01). At the final follow-up of the 135 surviving patients, the numbers of patients in CR, partial remission, and no remission were 126 (83%), five (3%), and one (1%) for AIHA and 119 (79%), eight (5%), and five (3%) for ITP, respectively (missing data in three cases). Forty-six patients (34%) had no treatment ongoing at last follow-up. No particular characteristic was associated with AIHA or ITP CR, including cIM and bIM.

Over the first three decades, the proportions of patients achieving sustained CR increased with age (Figure 1B). ITP and AIHA were in CR in 26% and 50% of cases at 10 years compared to 50% and 72% at 20 years, respectively (P<0.001 for both comparisons).

### Immunopathological manifestations

A total of 122 of 151 patients (81%) had at least one IM. The data for each category and specific diagnosis are shown in the Online Supplementary Table S2.

cIM developed in 100 of 151 patients (66%). A total of 47 patients (31%) had two or more IM and 22 (15%) patients had three or more IM (Online Supplementary Figure S2A). Patients with no cIM had shorter median follow-up times (9.7 years vs. 13 years; P=0.0002) and were younger when data were collected (15 years vs. 20 years; P<0.0001). A cIM was diagnosed before the first cytopenia in 21 of 100, simultaneously in 13, and after in 66 cases (median delay, 3.7 years [range, 0.2–20.5 years]; Figure 2A). Among the 185 cIM, 29 (16%) were diagnosed before any second-line treatment. No cIM category had a statistically significant difference in frequency before and after first-second-line treatment. The number of cIM increased

| Table 1. Patient characteristics. |
|----------------------------------|-------------------|
| **Number of patients**           | 151               |
| Sex ratio (male/female)          | 1.40 (88/63)      |
| Consanguinity, n (%)             | 12 (7.9)          |
| cIM/cancer in first-degree relative, n (%) | 43 (28)     |
| Median age (years) at            |                   |
| First cytopenia (min-max)        | 5.4 (0.2–16.0)    |
| ITP diagnosis (min-max)          | 6.7 (0.2–17.1)*   |
| AIHA diagnosis (min-max)         | 7.8 (0.2–21.5)*   |
| ES diagnosis (min-max)           | 8.9 (0.2–21.5)    |
| Sequence of ES                  |                   |
| Simultaneous, n (%)              | 52 (34.4)         |
| ITP then AIHA, n (%)             | 62 (41.1)         |
| AIHA then ITP, n (%)             | 37 (24.5)         |
| Time between first and second cytopenia (years) | 2.5 (0.1–15.8)   |
| Direct antiglobulin test at AIHA diagnosis | 74 (48.3)    |
| IgG, n (%)                       | 11 (7.3)          |
| IgA + C3, n (%)                  | 4 (2.6)           |
| Unspecified, n (%)               | 1 (0.7)           |
| Duration of follow-up after first cytopenia (years) | 18.5 (6.8–50.0)   |
| Age at last follow-up (years)    | 18.5 ± 6.0        |
| *P=0.0076. **Considering the 99 patients with sequential cytopenias. CIM: clinical immunopathological manifestation; Ig: immunoglobulin; SD: standard deviation; ITP: immune thrombocytopenic purpura; AIHA: autoimmune hemolytic anemia; ES: Evans syndrome.
with age. At 10 compared to 20 years old, 37% and 74% of patients had at least one cIM and 9% and 34% of patients had at least two cIM, respectively (P<0.001 for both comparisons; Figure 2B).

The most common cIM categories were lymphoproliferation (n=71), dermatological (n=26), gastrointestinal/hepatic (n=23) and pneumological manifestations (n=16; Figure 3, Online Supplementary Figure S2B). The most frequent cIM diagnosis were shown in Table 2. Thirteen patients developed a neurological manifestation as previously described.10

Four patients had a hematological malignancy (age at diagnosis): Hodgkin lymphoma (16 years), juvenile myelomonocytic leukemia (20 years), large granular lymphocytic leukemia (21 years) and angioimmunoblastic T-cell lymphoma (29 years). Older age at ES diagnosis (HR 1.09; 95% CI: 1.01–1.17; P=0.02), cIM/cancer in a first-degree relative (HR 1.64; 95% CI: 1.1–2.4; P=0.006), and the presence of AIN were independently associated with the number of cIM (HR 2.41; 95% CI: 1.5–3.8; P=0.0002).

Biological IM (bIM) were diagnosed in 101 of 151 patients (67%), and the frequency of bIM also increased with the age (Figure 2C). Hypogammaglobulinemia was the most frequently diagnosed bIM (n=54), including 44 cases diagnosed prior to any anti-CD20 treatment. Among those 54 patients, 25 (46%) received immunoglobulin replacement therapy. SLE and ALPS biomarkers were present (regardless of whether patients met the diagnostic criteria) in 42 and 24 patients, respectively. At 10 and 20 years of age, 39% and 75% of patients had at least one bIM, respectively (P<0.001).

Patients with bIM were more likely to have cIM (79% vs. 40%; P<0.001), and patients with cIM were more likely to have bIM (80% vs. 41%; P<0.001) but the correlation between the number of bIM and cIM was low (r=0.27; P<0.001).

Secondary pediatric-onset Evans syndrome

In 37 patients (24.5%), pES eventually revealed a SLE or a PID unknown at cytopenia onset.

Eleven patients (7.3%) eventually met the SLE SLICC diagnostic criteria.16 These patients were older at first cytopenia (median age 13 years vs. 5 years; P=0.007) and almost exclusively female (one of 88 males [1%] and ten of 63 females [16%]; P<0.001).
Seven patients (4.6%) met the diagnostic criteria for ALPS after pES onset which prompted targeted genetic analysis. Overall, 66 of 151 patients (44%) underwent genetic analyses as previously described. Among them, 26 (39%) patients were considered to have a PID (including the seven with ALPS). They carried a heterozygous pathogenic variant in CTLA4 (n=7), TNFRSF6 (germline n=6, somatic n=1), STAT3 (n=5), PIK3CD (n=1), CBL (n=1), and KRAS (somatic n=1) or a homozygous/compound heterozygous pathogenic variants in LRBA (n=3) and RAG1 (n=1). Compared to the 40 other patients, the 26 with a PID had more cIM (2 [range, 1-5] vs. 1 [range,
There was no statistically significant difference in the median time to ITP CR (4.7 years) vs. AIHA CR (5.5 years) (Wilcoxon–Mann–Whitney sum ranks comparison but was not significant, $P=0.26$). The number of patients receiving ongoing treatments also increased with age, particularly after the first decade ($P<0.0001$). The number of patients receiving ongoing treatments also increased with age ($P<0.0001$).

### Treatments

All except two patients (98.6%) had received at least one first-line treatment course. Second-line treatments (regardless of the hematological and/or extra-hematological indication) were required in 117 of 151 (77%) patients (Online Supplementary Figure 3A). Patients who did not receive any second-line treatment had shorter median follow-up times (10.5 years vs. 12.3 years; $P=0.017$). The median number of second-line treatments received was two (range, 0–9).

The number of second-line treatments received increased with the time elapsed since first cytopenia without reaching a plateau (Online Supplementary Figure 3B). After a sustained CR for both ITP and AIHA achieved, the number of treatments received had continued to increase: at 5 years after CR of both cytopenias, 67% of patients who achieved CR for both ITP and AIHA had received a new first and/or second-line treatments and 31% had received a new second-line treatment (Online Supplementary Figure S3C).

The number of second-line treatments received increased with age, particularly after the first decade (Figure 4A). At 10 and 20 years, 47% and 88% of patients had received a second-line treatment, respectively ($P<0.001$). The number of patients receiving ongoing treatments also increased with age (Figure 4B). At 10 and 20 years, 27% and 69% of patients had received an active second-line treatment, respectively ($P<0.001$). At the final follow-up, patients with a clm had received more second-line treatments (median, 3 vs. 1; $P<0.0001$).

The most frequently used second-line treatments were rituximab (n=79; 52%), azathioprine (n=55; 36%), splenectomy (n=36; 24%), and mycophenolate (n=29; 19%; Online Supplementary Table S3).

The number of clm was associated with a subsequent increase in the number of second-line treatments received (HR 1.4; 95% CI: 1.15–1.60; $P=0.0002$). On the contrary, the number of second-line treatment was not associated to a subsequent increase in the number of clm in univariate analysis (HR 1.09; 95% CI: 0.98–1.22; $P=0.11$).

### Infections

In total, 53 (35%) patients had severe or recurrent infections (Online Supplementary Table S4). The most frequent
were herpes zoster (n=17), sinusitis/otitis media (n=15), pneumopathy (n=12), and bronchiectasis (n=11). Patients with infections had more cIM (median, 2 vs. 1; P<0.0001), a higher incidence of hypogammaglobulinemia (53% vs. 28%; P=0.003), and received more second-line treatments (median 3 vs. 1; P<0.0001). Among the 16 patients with severe infection, nine (63%) were receiving an active treatment at infection time.

Severe/recurrent infections were independently associated with hypogammaglobulinemia (OR 2.4; 95% CI: 1.10–5.33; P=0.03) and the number of second-line treatments (OR 1.34; 95% CI: 1.13–1.71; P=0.002).

Mortality
Sixteen of the 151 patients followed for more than 5 years (10.6%) died, and seven other patients died before the fifth year of follow-up (23 deaths in total, 22 with available data). Patient survival at 5, 10, and 15 years after the first cytopenia was 97%, 92%, and 84%, respectively (Figure 5A). Mortality rates in patients with pES were higher than those in patients with cITP or AIHA alone (P<0.0001 for both comparisons).

Deaths occurred regularly throughout the follow-up period (median delay after first cytopenia diagnosis, 8.9 years [range, 0.1–24.3 years]) and at a median age of 18.0 years (range, 1.7–31.5 years) (Figure 5B). In the majority of these patients, cytopenia was under control at the time of death: 15 (65%) and 19 (83%) patients had CR or partial remission from ITP and AIHA, respectively (Figure 5C). Mortality was linked to the disease, the treatment, or both in eight (36%), two (9%), and twelve (55%) cases, respectively. The most frequent cause of death was infections (n=12 [52%]; Online Supplementary Table S5). Four patients (18%) died of a hemorrhage, and all were less than 13 years of age. The patients who died from a hemorrhage were younger than those who died from an infection (median 10 years vs. 18 years; P=0.05). All of these patients, except for one who died in the first month of a cerebral hemorrhage, had at least one cIM. Eight of the patients (36%) had hypogammaglobulinemia.

**Figure 4. Second-line treatments.** (A) Total number of second-line treatments received according to the age. (B) Number of second-line treatments ongoing according to age.
The patients who died had received more second-line treatments than the others in the cohort (median 3 vs. 2; \( P=0.02 \)), including splenectomy, which was more common in this subgroup (56% vs. 20%; \( P=0.003 \)). Patients who had received more than two second-line treatments had a three-fold increase in the risk of death compared to those who had received two or less (11 of 65 [16.9%] vs. five of 86 [5.8%], \( P=0.03 \)). At death, 81% of patients were receiving ongoing second-line treatment. The number of second-line treatments (HR 1.3; 95% CI: 1.1–1.6; \( P=0.004 \)) and severe/recurrent infections (HR 3.4; 95% CI: 1.2–9.7; \( P=0.02 \)) were independently associated with a higher risk of mortality after 5 years of follow-up.

Discussion

This large follow-up study of pES patients included more than 1,900 patient-years. Over the long term, AIHA and ITP were sustainably controlled in the majority of patients. Conversely, clinical and biological IM increased in frequency and number with increasing patient age, finally affecting almost all adult patients. The number of cIM was associated with a subsequent increase in the number of second-line treatments received. Mortality was high, frequently occurred while cytopenias were in remission, and most deaths concerned AYA. Two characteristics were associated to mortality: severe or recurrent infections and the number of second-line treatments received. Overall, the age-related clinical picture showed similar trends for all patients, shifting from cytopenia to increased IM, a greater treatment burden, and an increased risk of mortality.

In setting up a nationwide cohort, the CEREVANCE group tried to ensure unbiased patient inclusion in this study. Omitting patients with less than 5 years of follow-up data limited any bias due to short-term follow-up, which probably accounts for many of the discrepancies between previous studies. Indeed, our median follow-up period was more than twice as long as in previous studies.

Figure 5. Long-term survival. (A) Survival estimate of patients in terms of time from first cytopenia. At 10-year follow-up, survival rates among patients with chronic immune thrombocytopenic purpura (ITP) alone, autoimmune hemolytic anemia (AIHA) alone and pediatric-onset Evans syndrome (pES) were 100%, 99% and 92%, respectively. (B) Mortality is shown in terms of time from first cytopenia, as well as age. Individual values are shown as dots with medians and interquartile ranges shown as lines. (C) Hematological status at death. CR: complete remission; PR: partial remission; NR: no remission.
(median 4.8 years [range, 3–7 years]). However, although the trends reported here are clear, some factors may also influence the estimates. The loss to follow-up mainly concerned AYA and few patients were followed after the age of 20 years. As well, the CEREVERANCE group recommends clinical and biological follow-up at least every 6-12 months but local practice or patients’ phenotype (such as the presence of cIM) may have influenced biological testing.

Sustained CR was eventually achieved for both types of cytopenia in the vast majority of patients, although this often took many years, especially for ITP (>10 years for one-third of our patients). Because active treatments are used to treat most AYA (notably because of cIM), hematological CR may be drug induced and it is impossible to determine whether an underlying hematological autoimmunity is still present. The higher rate of sustained CR in ITP among patients with pES compared to patients with cITP alone may be due to more patients with pES receiving treatment.

One of the most striking findings in this study was the progressive increase in the frequency and number of IM. A range of cIM, affecting almost every organ, were identified and developed independently of cytopenias. These findings clearly show that pES is a marker for a more general tendency toward immunodeficiencies while we cannot exclude a contribution of the second-line treatments received to some IM. The underlying etiology is not completely understood and may vary among patients, with both genetic and environmental factors being important. Consequently, pES may be considered a composite syndrome with several overlapping subgroups of secondary pES. One of these subgroups includes patients with PID. Classically, ALPS has been associated with pES. In this study, only 4% of patients were diagnosed with ALPS based on well-defined criteria, despite evocative biological “ALPS-like” abnormalities in a larger proportion of patients. This observation is consistent with our previous study, which showed that more immune-response genes are potentially involved in pES than initially suspected. However, pES rarely comports as a Mendelian disease, and some of these variants may be predisposing rather than disease-causing alleles. Even in patients carrying a variant in a monogenic PID gene (e.g., TNFRSF6 or CTLA4), the altered genes show incomplete penetrance. We were unable to evaluate the proportion of patients who met common variable immunodeficiency disorders diagnostic criteria, as vaccine responses were not evaluable in all cases due to second-line treatments received. A second subgroup includes patients with SLE, although the prevalence of this subgroup is controversial. Our cohort suggests that SLE eventually occurs almost exclusively within the known at-risk population of female adolescents and is frequent in this subgroup, as it developed in seven of 15 (47%) of the females >12 years old. Despite its heterogeneity, the course of pES, in terms of age-related changes and trends, was similar for the majority of patients. The spectrum of IM described here is probably influenced by the underlying etiology, and further analyses are needed to understand the determinant of IM. The long-term follow-up of the present study confirms that the subgroup of patients with identified PID had more cIM.

Most patients required second-line treatments. These treatments reflect local practices and we cannot draw conclusions regarding their efficacy. We were unable to investigate the risk associated to specific treatments given the high heterogeneity in second-line treatment combinations and duration as well as the changes in management practices since the cohort onset in 2004. The rapid initial increase in second-line treatments is partly due to the high rate of early relapse and the current practice of administering steroid-sparing agents to treat pES. However, the presence of cytopenia is not the only reason for using these drugs and first- and second-line treatments were also used after CR of both cytopenias. cIM are important in determining the number of second-line treatments used, but bIM may also play a role, particularly in patients with SLE biomarkers, who are frequently given hydroxychloroquine. Nevertheless, second-line treatments are rarely selected based on a single factor. Patients with pES often have bIM and cIM, and the whole clinical picture needs to be assessed before selecting a treatment strategy. As previously reported, approximately one-third of patients may carry alterations in genes that are potentially accessible to targeted therapy. Given the high burden of second-line treatments and their association with infections and mortality, the CEREVERANCE network has proposed implementing genetic analyses for all patients with pES to limit the use of immunosuppressive and toxic drugs.

Comprehensively, the pES clinical picture changes as patients age. From 10 to 20 years of age, cytopenia tends to be controlled but IM are more prevalent, and active second-line treatments are used in more than two-thirds of patients during the pediatric-to-adult transition. Overall, as patients age, the illness becomes more severe and the risk of mortality increases. Both IM and treatment burden contribute to the infection-related mortality peak observed at the end of the second decade. The patients who died had received more second-line treatments, including splenectomy. Because these two parameters are correlated (r=0.60; P<0.0001), the number of deaths was too low to determine whether splenectomy alone was a risk factor of mortality per se or a marker of severity.

In conclusion, pES must now be considered a complex multi-systemic disease in which cytopenias frequently present fewer challenges than IM and infections in long-term follow-up. Adult patients with pES form a specific subgroup, distinct from older adults with ES. Multidisciplinary follow-up of patients with pES is needed and must focus on IM screening, genetic diagnosis, infections prevention, patient-tailored drugs development, and AYA management. Specifically, the infection burden may be reduced by ensuring up-to-date vaccinations, eradicating chronic infections, and using adequate antimicrobial prophylaxis or immunoglobulin replacements. As in several chronic pediatric diseases, dedicated child-to-adult transition programs are warranted to improve outcomes in patients with pES.

Disclosures
No conflicts of interest to disclose.

Contributions
TP, HF, TL, GL, and NA designed the study, analyzed the data and drafted the paper; TP and HF performed statistical analyses; CP and FR-L performed genetic analyses. All of the authors participated to prospective data collection and interpretation and revised the manuscript for critical content.
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