Correspondence

Hematology, University Hospital, Nantes, [10]IUC Oncopole, Toulouse, CRCT, [11]CRCNA, INSERM, CNRS, University of Nantes and [12]Site de Recherche Intégrée sur le Cancer (SIRIC) «ILIAD», Nantes, France.
E-mail: cyrille.touzeau@chu-nantes.fr

References

1. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2020;**95**(5):548–67.
2. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood*. 2007;**109**(8):3489–95.
3. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2014;**28**(5):1122–8.
4. Fonseca R, Abouzaid S, Bonafede M, Cai Q, Parikh K, Cosler L, et al. Trends in overall survival and costs of multiple myeloma, 2000–2014. *Leukemia*. 2017;**31**(9):1915–21.
5. Bruno AS, Willson JL, Opalinska JM, Nelson JJ, Lunacsek OE, Stafkey-Mailey DR, et al. Recent real-world treatment patterns and outcomes in US patients with relapsed/refractory multiple myeloma. *Expert Rev Hematol*. 2020;**13**(9):1017–25.
6. Giri S, Grimshaw A, Bal S, Godby KN, Kharel P, Djulbegovic B, et al. Efficacy of daratumumab in the treatment of multiple myeloma with high-risk cytogenetics: meta-analysis of randomized phase III trials. *J Clin Oncol*. 2020;**38**(15_suppl):8540.
7. Corre J, Montes L, Martin E, Perrot A, Caillot D, Leleu X, et al. Early relapse after autologous transplant for myeloma is associated with poor survival regardless of cytogenetic risk. *Haematologica*. 2019;**105**(9):e480–483.
8. Thakurta A, Ortiz M, Blecua P, Towfic F, Corre J, Serbina NV, et al. High subclonal fraction of 17p deletion is associated with poor prognosis in multiple myeloma. *Blood*. 2019;**133**(11):1217–21.
9. Perrot A, Lauwers-Cances V, Tournay E, Hulin C, Chretien M-L, Royer B, et al. Development and validation of a cytogenetic prognostic index predicting survival in multiple myeloma. *J Clin Oncol*. 2019;**37**(19):1657–65.
10. Perrot A, Lauwers-Cances V, Corre J, Robillard N, Hulin C, Chretien M-L, et al. Minimal residual disease negativity using deep sequencing is a major prognostic factor in multiple myeloma. *Blood*. 2018;**132**(23):2456–64.
11. Moreau P, Attal M, Caillot D, et al. Prospective evaluation of magnetic resonance imaging and [^{18}F]Fluorodeoxyglucose positron emission tomography-computed tomography at diagnosis and before maintenance therapy in symptomatic patients with multiple myeloma included in the IFM/DFCI 2009 trial: results of the IMAJEM study. *J Clin Oncol*. 2017;**35**(25):2911–8.
12. Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;**376**(14):1311–20.
13. Hari P, Pasquini MC, Stadtmauer EA, Fraser R, Fei M, Devine SM, et al. Long-term follow-up of BMT CTN 0702 (STaMINA) of postautologous hematopoietic cell transplantation (autoHCT) strategies in the upfront treatment of multiple myeloma (MM). *J Clin Oncol*. 2020;**38**(15_suppl):8506.
14. Gagelmann N, Eikema DJ, de Wreede LC, Rambaldi A, Iacobelli S, Koster L, et al. Upfront stem cell transplantation for newly diagnosed multiple myeloma with del(17p) and t(4;14): a study from the CMWP-EBMT [published online ahead of print, 2020 Jul 24]. *Bone Marrow Transplant*. 2021;**56**(1):210–7.
15. Shah N, Chari A, Scott E, Mezzi K, Usmani SZ. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. *Leukemia*. 2020;**34**(4):985–1005.
16. Gagelmann N, Riecken K, Wolschke C, Berger C, Ayuk FA, Fehse B, et al. Development of CAR-T cell therapies for multiple myeloma. *Leukemia*. 2020;**34**(9):2317–32.

Splenectomy for haemophagocytic lymphohistiocytosis of unknown origin: risks and benefits in 21 patients

Sporadic haemophagocytic lymphohistiocytosis (HLHs) develops in adults with no hint of a family history but in a context of associated diseases (HLHs-AD) classified as malignant (M-HLHs), autoimmune (AI-HLHs), or none/idiopathic (I-HLHs).[1] Infectious events are strong stimuli that boost HLHs onset. HLHs outcomes are usually very poor, especially in the case of M-HLHs[2] compared to other ADs.[3,4] Thus, early identification of any HLHs-AD is the cornerstone of HLHs management in adults and splenectomy can be the only strategy available for obtaining a histological diagnosis.[5] However, this procedure is still controversial and may be difficult to perform in these often very frail patients.[6,7] The purpose of this study was to evaluate the operative risk, the benefit in terms of HLHs-AD diagnosis and the outcomes of splenectomy in 21 adult patients with secondary HLH without an underlying diagnosis.

HLH patients who underwent splenectomy from 2002 to 2018 were retrospectively included using the French HLHs study group and HLH-GENE cohort database.[8] Inclusion criteria are developed in Table SI.[9] Infections were considered as triggers of HLH onset. This study was approved by the local ethics committee of Avicenne Hospital (CLEA-2018-50). Values were compared using the two-tailed Fisher exact test.

Twenty-one patients were included, the median H-score probability was 98% (range 52·2–99·94%).[10] The median age at diagnosis was 63 years (range 20–83). Extensive investigations before splenectomy are presented in Table I. Seven patients were tested positive for Epstein–Barr virus using the polymerase chain reaction (EBV-PCR), and all patients underwent computed tomography (CT) scans and positron emission tomography (PET) imaging scans.

638

Table I. Patients' characteristics ($n = 21$).

Details of clinical, biological, infectious and histological investigations performed in HLH patients before splenectomy	Whole cohort, $n = 21$
Clinical characteristics	
Age at diagnosis, median (range)	63 (20–83)
Sex ratio; H/F	1·33 (12/9)
Fever, n (%) (peak temperature of >38·5°C for >7 days)	20 (95)
Splenomegaly, n (%) (spleen palpable >3 cm below costal margin)	19 (90)
Comorbidities*	
Cardiovascular comorbidities, n (%)	4 (19)
Cardiovascular risk factors, n (%)	7 (33)
Previous history of severe infection, n (%)	5 (24)
Auto-immune diseases, n (%)	5 (24)
Immunosuppression, n (%)	4 (19)
Previous history of cancer, n (%)	4 (19)
Charlson Comorbidity Index, mean (range)	4 (0–10)
Biological characteristics, mean (range)	
Haemoglobin (g/dl)	9·0 (6·8–11·3)
Leucocytes (/mm^3)	5 821 (900–18 300)
Neutrophils (/mm^3)	3 176 (400–11 000)
Lymphocytes (/mm^3)	908 (100–3 800)
Platelets (/mm^3)	82 429 (4 000–271 000)
Fibrinogen (g/l)	3·9 (1·8–10·5)
Triglyceridaemia (g/l)	3·3 (1·5–5·7)
Serum ferritin (ng/ml)	13 959 (1 108–83 000)
LDH (iu/l)	1 096 (280–3 147)
Beta-2-microglobulin (mg/l)	5·8 (2·5–12·6)
CRP (mg/l)	142 (31–421)
H-score	
H-score probability: median (range)	98 (52·2–99·94)
H-score: median (range)	231 (169–288)
Extensive check-up before splenectomy	
Infectious check-up: positive results/done, n	
Non EBV herpes virus (PCR) (HSV, VZV, CMV, HHV6, HHV8)	1 (CMV)/17
EBV (PCR) ($\geq$ 2 log/ml)	7/19
HIV	1/21
Blood cultures	0/15
Search for Leishmania, Mycobacteria	0/15
Haematological check-up, positive results/done, n	
Hypogammaglobulinaemia/immunophenotyping (n)	3/16
Clonality	5/16
Haemophagocytosis (n)/medullar aspiration (n)	14/21
Haemophagocytosis (n)/bone marrow biopsy (n)	2/19
Scanner, $n = 21$	
Splenomegaly, n (%)	17 (81)
Median spleen size (range) in case of splenomegaly	16·5 (14–18)
Hepatomegaly, n (%)	18 (86)
PET scanner, $n = 18$	
Spleen: SUVmax	22·1
Liver: SUV max	12
Other biopsies (lymph node, liver, lung, skin, accessory salivary glands, intestine), n (%)**	15 (71)
Treatment of HLH before splenectomy, n (%)	
Corticosteroids	16 (81)
Intravenous immunoglobulin	6 (29)
Etoposide	9 (43)
Anti-infectious agent	8 (38)
Other (anti-IL1 (Anakinra), anti-CD20 (Rituximab), ciclosporin)	3 (14)

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Table I. (*Continued*)

Details of clinical, biological, infectious and histological investigations performed in HLH patients before splenectomy	Whole cohort, $n = 21$
Severe HLH, *n* (%)	
Relapse/refractory to HLH treatment	20 (95)
Transfer to ICU before splenectomy	1 (4·7)
Transfer to ICU after splenectomy	5 (24)

HLH, haemophagocytic lymphohistiocytosis; LDH, lactase dehydrogenase; CRP, c-reactive protein; EBV, Epstein–Barr virus; PCR, polymerase chain reaction; HSV, herpes simplex virus; VZV, varicella-zoster virus; CMV, cytomegalovirus; HHV, human herpesvirus; HIV, human immunodeficiency virus; PET, positron emission tomography; SUV, standardized uptake value; ICU, intensive-care unit.

*For more information, see supplementary data. Charlson comorbidity index: Charlson, Pompei, Ales, & Mackenzie, 1987; Elixhauser, Steiner, Harris, & Coffey, 1998.

**Among the six patients who did not undergo attempted diagnostic lymph node biopsy before splenectomy, there was no significant adenomegaly on CT scan for five patients. For the last patient, only deep adenomegalies were identified on CT scan, too difficult to access surgically.

Table II. Results of splenectomy (*n* = 21). Twenty-one patients were studied in terms of associated disease, infectious booster, treatment, mortality and follow-up after splenectomy for undiagnosed HLHs.

Sex	Age at HLH	Immune deficiency before splenectomy	Associated disease (AD)	Details	Treatment post splenectomy	Death	Length of follow up (months)
M	28	No	Idiopathic	No infection	Allogeneic bone marrow transplantation	No	16
M	28	No	Idiopathic	No infection	Allogeneic bone marrow transplantation	No	49
F	51	No	Idiopathic	*Mycobacterium tuberculosis*	Anti-tuberculosis	No	16
F	71	Corticosteroids for Evans syndrome	Idiopathic	*Mycobacterium abcessus*, PCR EBV+	Not documented	No	7
M	40	No	Idiopathic	Nocardiosis, PCR EBV+	Yes	No	39
M	75	No	Idiopathic	Leishmaniasis, PCR EBV+	Yes	No	10
M	43	No	Idiopathic	No infection	Favourable post splenectomy	No	14
M	44	HIV*, HCV*	Idiopathic	PCR EBV+	Favourable post splenectomy	No	3
M	64	Kidney Transplantation Liver Transplantation	Idiopathic	No infection	No	Yes	3
F	63	No	Idiopathic	No infection	No	Yes	5
F	53	No	Malignancy-AD	DLBCL	Chemotherapy	No	28
M	45	No	Malignancy-AD	DLBCL	Chemotherapy	No	6
M	83	No	Malignancy-AD	DLBCL, PCR EBV+	No	Yes	2
M	79	No	Malignancy-AD	DLBCL	No	Yes	1
F	79	No	Malignancy-AD	DLBCL, PCR EBV+	Chemotherapy	No	6
M	69	DLBCL 4 years, CR	Malignancy-AD	DLBCL	Chemotherapy	No	6
F	60	No	Malignancy-AD	Intravascular large B cell lymphoma, EBV-	Chemotherapy	Yes	8
F	68	No	Malignancy-AD	Peripheral T-cell lymphoma, EBV+	Chemotherapy	Yes	4
F	69	No	Malignancy-AD	Castleman disease, HHV8+	Anti-CD20	No	73
M	65	No	Malignancy-AD	Angioimmunoblastic T-cell lymphoma, PCR EBV+	Chemotherapy	No	16
F	20	No	Auto-Immune-AD	Kikuchi syndrome	Corticosteroids, hydroxychloroquine	No	1

HIV, human immunodeficiency virus; HCV, hepatitis C virus; PCR, polymerase chain reaction; EBV, Epstein–Barr virus; HHV, human herpesvirus; DLBCL: diffuse large B-cell lymphoma, CR: complete response.
*Controlled viral load.

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Hepatosplenomegaly was the main abnormality (n = 17) and the median maximum standardized uptake value (SUVmax) values observed in the spleen, liver or lymph nodes were 6·5 (range 0–22·1), 3·3 (0–12) and 7·6 (0–28), respectively. Overall, the HLHs were severe, all needed to be treated and 20/21 relapsed. The median time between the HLHs diagnosis and splenectomy was 2·3 months (range 0–8·7 months).

Histological analysis revealed nine cases of non-Hodgkin lymphoma [NHL; EBV+ T NHL (n = 2) and EBV− B NHL (n = 7)], one case of Castleman disease and one case of Kikushi disease for a total of 10/21 neoplastic M-HLHs and 1/21 AI-HLHs. In 10/21 patients, the histological lesions were non-specific except, specifically in this group, the presence of haemophagocytosis; patients were thus classified as having idiopathic I-HLHs. In four of them, microbiological analysis revealed intracellular infectious triggers: intracellular mycobacteria (n = 2), leishmaniasis (n = 1), or nocardiosis (n = 1), including three patients also positive for EBV-PCR in the blood (Table II).

Splenectomy was performed by laparoscopy procedure in eight patients, t of whom had to be converted to laparotomy, and by laparotomy in the other 13 patients. The presence of a massive splenomegaly (>17 cm) was associated to an increased risk of morbidity following splenectomy. Operative mortality reached 9·5% (2/21), concerning the oldest patients of the cohort (79 years old and 83 years old); both had cardiopathy and histologically diffuse large B-cell lymphoma. Morbidity was 14·5% (3/21).

Thus, 19/21 patients were alive after splenectomy. The eight M-HLHs patients were treated following adapted protocols. Two patients died during treatment (T/B NHL: 1/1) at four and eight months after splenectomy, and two were alive after completing treatment (Castleman disease n = 1, T NHL n = 1, B NHL n = 4), with no HLH or NHL relapse with a median follow-up at 11 months. Two I-HLHs patients died despite receiving several lines of HLH treatment at three and five months post splenectomy. The others were alive with a median follow-up of 15 months. Among the eight I-HLHs, four had identified infectious triggers and were treated with a favourable outcome, two resolved spontaneously following splenectomy, and in two other cases, HLHs relapses resolved after atopoietic stem cell transplantation and they were alive with a median follow-up of 33 months (Figure S1). Data collected were compared between patients with M-HLHs and the others (AI or I-HLHs). M-HLHs patients were older (68 vs 44 years, P = 0·01) and had a higher number of lymphocytes (1509 vs 440, P = 0·02) (Table SII).

In HLH, splenectomy has long been considered too dangerous due to the frequent presence of cytopenia and coagulopathy.[6,7] In our series, operative mortality was 9·5% and morbidity was 14·3%. The two patients who died were over 70 years old and had aggressive lymphoma. Despite the small size of the cohort, these results seem in accordance with previous data concerning splenectomy in patients without

HLH.[11] Moreover, operative risk was evaluated in a retrospective study of 100 HLH adult patients with no differences in terms of survival in the splenectomy and non-splenectomy groups, indicating that splenectomy itself does not shorten the survival of patients with HLH.[5] Therefore, HLH may not represent an additional risk of morbidity/mortality for splenectomy, which should be confirmed in a larger study. However, the benefit/risk should be evaluated cautiously in each case.

Here, splenectomy classified all 19 live patients into three distinct groups, idiopathic including associated infectious triggers, malignancy and autoimmune, and allowed for adapted treatment for 17 of them.[12] This high rate of diagnosis allowed by splenectomy is in line with previous reports.[13] Moreover, surgery spontaneously resolved HLH in two idiopathic HLHs. This partially explains the better outcomes of HLHs who underwent splenectomy compared to those who did not, as has been previously reported.[5] M-HLHs was treated in six out of eight patients with favourable outcomes, contrasting with previous reports about M-HLHs.[2] Thus, in the case of lymphoma, a 'partial therapeutic effect' of surgery on M-HLHs itself, by removing the tumour mass located in the spleen, could partially contribute to lymphoma/M-HLHs treatment. In two cases of I-HLHs, patients who underwent an equivalent form of 'primitive/genetic HLH' were successfully treated by bone marrow transplantation. Considering the heterogeneity of HLHs-AD, the identification of the cause of HLHs-AD is necessary before proposing an appropriate treatment.

In conclusion, splenectomy has a real diagnostic benefit in establishing the cause of HLHs-AD and may also have a therapeutic effect. The surgical risk may not be increased in the presence of HLHs, even in cases of relapse.

Competing interests

The authors have no competing interests to declare in relation to this manuscript.

Guillemette Fouquet[1] (ID)
Claire Larroche[2]
Benjamin Carpentier[3]
Louis Terriou[4]
Geoffrey Urbanski[5,6]
Carole Lacout[6]
Estibaliz Lazaro[7,8]
Charlotte Salmon Gandonnière[9]
Antoinette Perlat[10]
Francois Lifermann[11]
Nanthara Sritharan[12]
Fabrice Bonnet[13]
Olivier Hermine[1,14]
Coralie Bloch-Queyrat[1,15]

[1]Laboratory of cellular and molecular mechanisms of hematological disorders and therapeutic implications, INSERM U1163, Imagine Institut,

Correspondence

Sorbonne Paris University, Paris, [2]Internal Medicine, Groupe Hospitalier Paris Seine Saint Denis, Hôpital Avicenne, AP-HP, Bobigny, [3]Hematology Department, Saint-Vincent Hospital, GHICL, [4]Service de Médecine Interne et Immunologie Clinique, Centre de référence des maladies autoimmunes systémiques rares du Nord et Nord-Ouest de France (CeRAINO), Univ. Lille, Inserm, CHU Lille, U1286 - INFINITE - Institute for Translational Research in Inflammation, F-59000, Lille, [5]UMR CNRS 6015-INSERM U1083, Mitolab Team, MITOVASC Institute, University, [6]Department of Internal Medicine, Angers University Hospital, Angers, [7]CNRS-UMR 5164 Immuno ConcEpT, Bordeaux University, [8]Department of Internal Medicine, Bordeaux University Hospital, Bordeaux, [9]Intensive Care Medicine, INSERM CIC 1415, CRICS-TriggerSep Research Network, CHRU de Tours, 37044, Tours, [10]Internal Medicine and Clinical Immunology, CHU Rennes, Rennes, [11]Internal Medicine and Hematological Unit, Centre Hospitalier de Dax, Dax, [12]Departement of Clinical Research, Paris Seine Saint Denis Hospital, Sorbonne Paris University, AP HP, Bobigny, [13]CHU de Bordeaux, Hôpital Saint-André, Service de Médecine Interne et Maladies Infectieuses and Université de Bordeaux, INSERM U1219, BPH, F-3300, Bordeaux, [14]Department of Clinical Hematology, Necker Children's Hospital, AP HP, Paris and [15]Departement of Clinical Research, Paris Seine Saint Denis Hospital, Sorbonne Paris University, AP HP, Bobigny, France.
E-mail: coralie.bloch-queyrat@aphp.fr

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. HLH diagnosis criteria (adapted from the HLH-2004 diagnostic criteria [9]).

Table SII. Patient characteristics and imaging tests according to the diagnosis.

Fig. S1. Study Flowchart.

References

1. Hayden A, Park S, Giustini D, Lee AYY, Chen LYC. Hemophagocytic syndromes (HPSs) including hemophagocytic lymphohistiocytosis (HLH) in adults: a systematic scoping review. *Blood Rev.* 2016;**30**(6):411–20.
2. Daver N, McClain K, Allen CE, Parikh SA, Otrock Z, Rojas-Hernandez C, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. *Cancer.* 2017;**123**(17):3229–40.
3. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol.* 2015;**90**(3):220–4.
4. Birndt S, Schenk T, Heinevetter B, Brunkhorst FM, Maschmeyer G, Rothmann F, et al. Hemophagocytic lymphohistiocytosis in adults: collaborative analysis of 137 cases of a nationwide German registry. *J Cancer Res Clin Oncol.* 2020;**146**(4):1065–77.
5. Ma J, Jiang Z, Ding T, Xu H, Song J, Zhang J, et al. Splenectomy as a diagnostic method in lymphoma-associated hemophagocytic lymphohistiocytosis of unknown origin. *Blood Cancer J.* 2017;**7**(2):e534.
6. Cho SG, Koh YB, Chang HS, Park G, Kang CS, Park JW, et al. Successful treatment with splenectomy and interferon alpha against recurred hemophagocytic syndrome in remission state of anaplastic large cell lymphoma following high-dose therapy and autologous peripheral blood stem cell transplantation. *Eur J Haematol.* 2005;**74**(3):259–62.
7. Zhang L-J, Zhang S-J, Xu JI, Li J-Y, Wang L-L, Hu Y-X, et al. Splenectomy for an adult patient with refractory secondary hemophagocytic lymphohistiocytosis. *Biomed Pharmacother.* 2011;**65**(6):432–5.
8. Garcelon N, Neuraz A, Salomon R, Faour H, Benoit V, Delapalme A, et al. A clinician friendly data warehouse oriented toward narrative reports: Dr. Warehouse. *J Biomed Inform.* 2018;**80**:52–63.
9. Henter J-I, Horne AnnaCarin, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;**48**(2):124–31.
10. Hejblum G, Lambotte O, Galicier L, Coppo P, Marzac C, Aumont C, et al. A web-based delphi study for eliciting helpful criteria in the positive diagnosis of hemophagocytic syndrome in adult patients. *PLoS One.* 2014;**9**(4):e94024.
11. Bagrodia N, Button AM, Spanheimer PM, Belding-Schmitt ME, Rosenstein LJ, Mezhir JJ, et al. Morbidity and mortality following elective splenectomy for benign and malignant hematologic conditions: analysis of the American College of Surgeons National Surgical Quality Improvement Program data. *JAMA Surg.* 2014;**149**(10):1022–9.
12. Ciftciler R, Pasayeva A, Aksu S, Ozcebe O, Sayınalp N, Malkan UY, et al. Indications and Outcomes of Splenectomy for Hematological Disorders. *Open Med (Wars).* 2019;**14**:491–6.
13. Jing-Shi W, Yi-Ni W, Lin WU, Zhao W. Splenectomy as a treatment for adults with relapsed hemophagocytic lymphohistiocytosis of unknown cause. *Ann Hematol.* 2015;**94**(5):753–60.

Characteristics and outcome of human immunodeficiency virus (HIV)-associated primary effusion lymphoma as observed in the German HIV-related lymphoma cohort study

Human immunodeficiency virus (HIV)-associated primary effusion lymphoma (PEL) is a rare and aggressive subtype of B-cell non-Hodgkin lymphoma (NHL).[1,2] PEL usually arises in body cavities but may also present as extracavitary lesions without effusion (solid variant). Only a limited number of studies and case series on HIV–PEL have been published but