Received: 1 October 2023 | Revised: 7 December 2023 | Accepted: 18 December 2023

DOI: 10.1002/jha2.841

eJHaem

British Society for Haematology

CASE REPORT

Atypical meningeal localization of classical hairy cell leukemia with an impressive response to rituximab and cladribine association. A case report and literature review

Fabien Claves[1,2] | Sylvain Carras[1,2,3,4] | Barbara Burroni[5] | Elsa Maitre[6,7] | Jean Boutonnat[8] | Xavier Troussard[6,7,9] | Lysiane Molina[1]

[1]Hematology Department, University Hospital of Grenoble Alpes, Grenoble, France

[2]Grenoble Alpes University, Grenoble, France

[3]Genetic of Hematological Malignancies Department, University Hospital of Grenoble, Grenoble, France

[4]Institute for Advanced Biosciences, Grenoble, France

[5]Pathology Department, Cochin University Hospital, Paris, France

[6]University Hospital Caen, Caen, France

[7]INSERM U1245, Normandie University, Caen, France

[8]Pathology Department, University Hospital of Grenoble Alpes, Grenoble, France

[9]Hematology Department, University Hospital Caen, Caen, France

Correspondence
Fabien Claves, Hematology Department, University Hospital of Grenoble Alpes, Grenoble, France.
Email: fclaves@chu-grenoble.fr

Abstract

Hairy cell leukemia (HCL) is a rare lymphoproliferative disorder classically presenting with cytopenia and recurrent infections but atypical manifestations such as bone lesions, skin lesions and effusion have been described.

We report here an unusual meningeal localization in a 33 years old man who presented with headache, hand paresthesia and visual symptoms. Brain magnetic resonance imaging revealed an occipital meningeal lesion. Diagnostic explorations led to the diagnosis of classical HCL with meningeal localization. After treatment by cladribine and rituximab the patient rapidly improved and is still in complete remission 12 months after end of treatment.

The literature review identified 9 other cases of HCL with central nervous system localization (CNS) presenting with brain parenchyma and/or meninges localization. Four out of 9 patients presented with hyperleukocytosis. Most patients experienced good responses with various treatments. Cladribine alone or with rituximab led to complete responses similar to our patient. In our patient, molecular biology revealed KLF2 mutations, which implication in the atypical localization could be suspected but would need dedicated studies.

In conclusion, CNS localizations of HCL are rare but can be observed and treatment with cladribine alone or with rituximab appears as an effective strategy.

KEYWORDS

atypical localization, central nervous system, cladribine and rituximab, Hairy cell leukemia

Hairy cell leukemia (HCL) is a rare B-cell malignancy, with 1.100 new patients each year in the United States. HCL mostly involves men with a 4 to 1 ratio and a median age of 60 years old. Frequent manifestations at diagnosis include infections, splenomegaly, and/or cytopenias [1]. Classical HCL must be differentiated from other HCL-like disorders like hairy cell leukemia variant, splenic diffuse red pulp lymphoma, or splenic marginal zone lymphoma. Classical HCL cells express characteristic markers: CD11c, CD25, CD103, and CD123. Expression of at least three of these markers is required for the diagnosis and is considered a surrogate of the disease [2]. Purine nucleoside analogs are

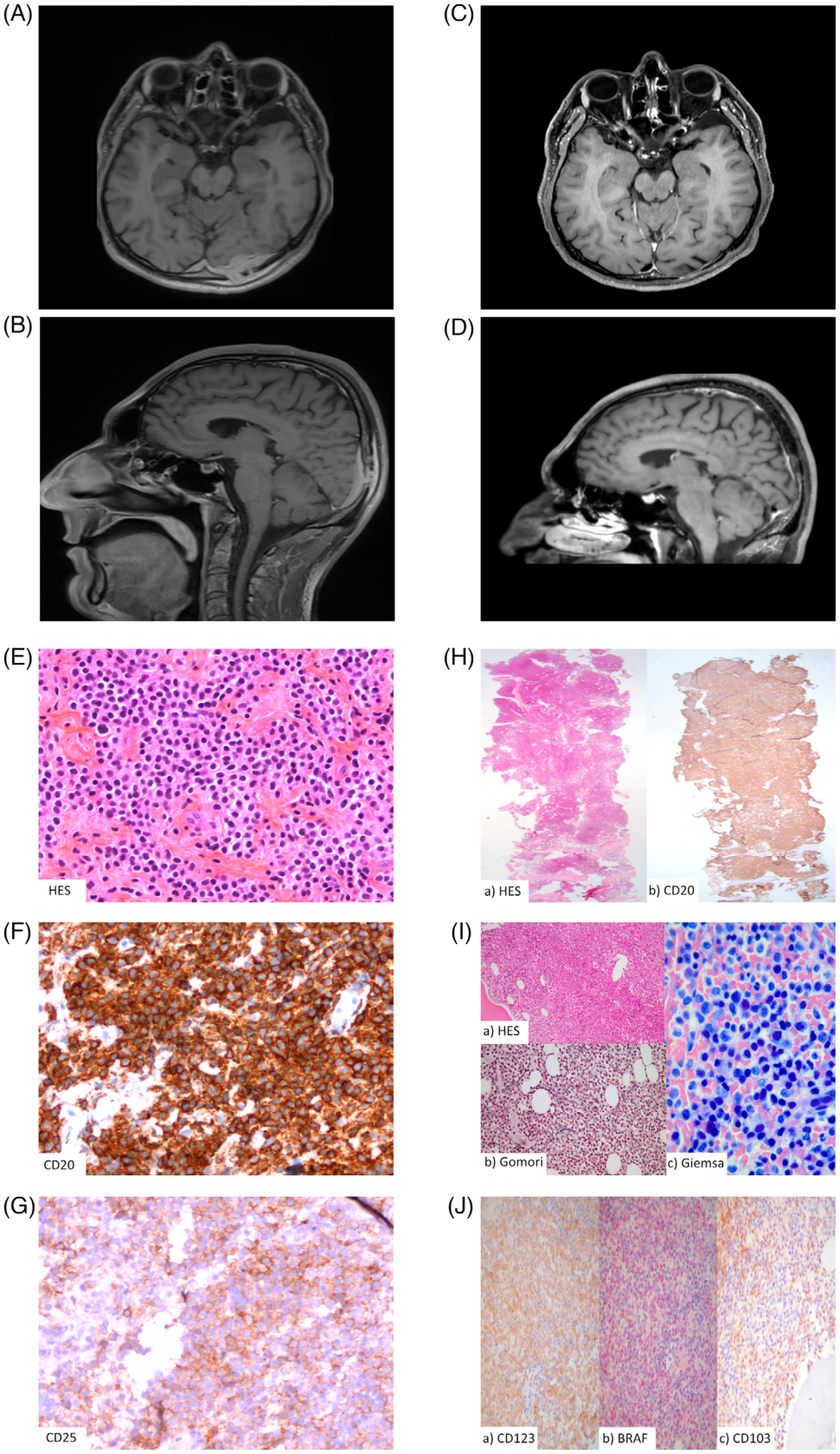

FIGURE 1 (A, B) Magnetic resonance imaging (MRI) at diagnosis showing the parieto-occipital lesion in T1 sequences, axial (A), and sagittal (B). (C, D) MRI at 3 months post-treatment, T1 sequences with gadolinium injection, axial (C), and sagittal (D). (E–G) Meningeal biopsy. (E) Meningothelial tissue infiltrate in Hairy cell leukemia (HCL) is diffuse and does not form nodular aggregates. The hairy cells appear round and monotonous. The cytoplasm appears clear and hairy projections are not evident on routine Haematoxylin-Eosin Saffron (HES) staining (×200). (F) All the cells show strong and membranous labeling with B cell markers such as CD20 (×200). (G) Most of the cells are labeled with CD25 from a

the standard of care therapy for symptomatic HCL, with high complete response rates (80-90%) and a 90% overall survival at 10 years. However, 50% of the patients will eventually relapse within 5 years of frontline treatment and will require subsequent therapy [1, 3, 4].

It has been described that Hairy cell leukemia (HCL) can rarely manifest with atypical clinical findings, such as lytic bone lesions, effusions, skin lesions, bulky mass as well as autoimmune complications [5–7]. We report here an unusual case of classical HCL with meningeal localization at diagnosis.

A 33-year-old man began to complain of constant headaches in the occipital area associated with short-lasting crises of dizziness. In January 2022, the symptoms worsened with intermittent bilateral hand paresthesia and recurrent episodes of right lateral homonymous hemianopsia. Neurological examination at that time was strictly normal between crises. There was no altered general state or B symptoms. Clinical examination found isolated splenomegaly (6 cm below the costal margin). A brain magnetic resonance imaging (MRI) was performed and revealed osteolysis with a contiguous parieto-occipital lesion (Figure 1A,B). This meningeal lesion measured 10 mm in width and 60 mm in height.

Laboratory tests showed minor nonregenerative normocytic anemia (12 g/dL), monocytopenia, normal platelets, and total white blood cell count with the presence of 12% of atypical lymphocytes (0.25 G/L). Peripheral blood lymphocyte immunophenotyping by flow cytometry found a monotypic population CD20 (+), lambda (+), CD5 (-), CD10 (+) with strong expression of CD25, CD11c and CD103 in favor of classical HCL. Given the unusual localization, a meningeal biopsy was performed and concluded a localization of the HCL (Figure 1E–G). Bone Marrow aspirate immunophenotyping by flow cytometry was as follows: CD20 (+), CD5 (-), CD10 (+), CD23 (-), CD25 (+), CD11c (+) and CD103 (+). Cerebro-spinal fluid evaluation by cytology and flow cytometry did not reveal HCL cells. A bone marrow biopsy confirmed a massive infiltration (90%) by the HCL cells. By immunohistochemistry on paraffin-embedded tissues, tumor cells were CD20 (+), CD25 (+), DBA44 (+/-), Annexin A1 (+/-), CyclineD1 (-/+), CD5 (-), SOX11 (-), CD200 (+), CD103 (+), CD123 (+) and BRAFp.V600E (+) (Figure 1H–J.) 18F-fluorodeoxyglucose positron emission tomography scan (PET scan) exhibited mild hypermetabolism of the spleen, coelio-mesenteric and lombo-aortic lymph nodes (SUVmax: 5,1) as well as diffuse bone marrow hypermetabolism.

Regarding molecular biology, the mutational status of the Immunoglobulin heavy chain locus revealed a VH1-69 rearrangement with a mutated status (93% of homology) in the blood, bone marrow, and meningeal biopsy. Next-generation sequencing analysis (NGS) of the three samples found a *BRAF* V600E mutation accompanied by a synonymous *BRAF* mutation on the same allele (*BRAF* A598) and mutation of *KLF2* in the known S275N hotspot as well as *KLF2* intronic mutations. Lastly, only the meningeal biopsy displayed an additional intronic mutation of *KLF2* on an AID motif (variant allele frequency of 36%).

Altogether, a diagnosis of classical hairy cell leukemia was retained, although the central nervous system (CNS) localization was atypical. The patient started treatment with rituximab and cladribine (8 cycles of weekly injection of rituximab and one course of subcutaneous cladribine for 5 days) in May 2022. Neurological symptoms rapidly improved upon treatment initiation with the patient achieving full clinical recovery as well as correction of cytopenias. At three months post-treatment evaluation, blood and marrow immunophenotyping by flow cytometry revealed no tumoral cells. No tumoral cells were identified in the bone marrow biopsy. Brain MRI showed near complete regression of the lesion and the PET scan was negative (Figure 1C,D).

This unusual case described an uncommon presentation of HCL. CNS localizations of HCL have rarely been reported and we describe here an exhaustively documented case, including molecular data. Indeed, few cases with CNS localizations were reported and are summarized in Table 1, with involvement of the brain parenchyma and/or meninges. It is interesting to note that 4/9 cases exhibited hyperleukocytosis at diagnosis. Most patients experienced good responses to various treatments. Our patient demonstrated a fast and impressive response to rituximab and cladribine treatment. Twelve months after treatment completion the patient is still in complete remission. Cladribine is highly efficient in HCL and is known for its efficient passage of the blood-brain barrier (BBB). Thus, cladribine could be particularly interesting in treating CNS localization of HCL. Rituximab BBB penetration is lower but the association with cladribine has been proven to be very effective in HCL according to recent data [1]. In our case, a deep systemic and meningeal control of the disease was obtained.

There is little data regarding the molecular biology of these atypical CNS localizations. Our patient harbors the classical *BRAF V600E* mutation but also mutations in the *KLF2* gene. *KLF2* is the second most mutated gene in HCL and encodes for Krüppel-like factor 2 which is an important factor for B-cell homing to lymph nodes as well as a negative regulator of the NFκB pathway [8]. KLF2 knockdown in a murine model led to reduced trafficking function and blood recirculation of B cells [9]. One could hypothesize that additional mutational hits on *KLF2* could further impair HCL cell trafficking ability and thus could explain the atypical localization. Unfortunately, there is a lack of molecular data from the other described cases thus it would be very interesting to gain insight into the genomic landscape of these uncommon patients.

weak to a bright intensity (×200). (H–J) Trephine bone marrow biopsy at diagnosis. H(a): massive diffuse infiltration (×1.25). H(b): by immunohistochemistry on paraffin-embedded tissues, tumor cells are strongly CD20 positive (×1.25). I: Morphological details on bone marrow core biopsy. I(a): interstitial infiltration of small lymphocytes with abundant cytoplasm with variable preservation of background hematopoietic elements, HES stain (×200). I(b): Gomori stain shows a little reticulum fibrosis (×400). I(c): Giemsa stain shows a characteristic "fried-egg" appearance with abundant cytoplasm and extravasated erythrocytes surrounded by neoplastic cells. Some typical mast cells could be observed (×1000). J(a, b, c): By immunohistochemistry, tumor cells were strongly positive for CD123 (a), BRAF (b), and CD103 (c) (×400).

TABLE 1 Literature review of Hairy cell leukemia (HCL) cases with central nervous system (CNS) localization.

PMID	Age / Sex	Diagnosis or relapse	Prior therapy for HCL	Clinical presentation	Biological presentation	Brain parenchymal or meningeal localization	Hairy cells in CSF	Phenotype	Molecular biology	Treatment	Response
23439755	51/M	D	–	Confusion, aphasia, hepatomegaly, splenomegaly	Hyperleucocytosis (60 G/L), anemia, thrombocytopenia	Brain parenchymal (supra-tentorial)	Not tested	CD11c+ CD25+ CD103+ CD10- CD5-	NA	HD MTX + HD steroids + CDA 7 days	NA (death from GI bleeding)
29296733	42/M	D	–	Headache, lymphadenopathy, splenomegaly	Hyperleucocytosis (37 G/L), anemia, thrombocytopenia	Brain parenchymal (supra and infra-tentorial)	Not tested	CD11c+ CD25+ CD103+	BRAF V600E	CDA 5 days + Ri (8 injections weekly)	CR
3964107	35/M	D	–	Meningeal syndrome	NA	Both (autopsy)	No	NA	NA	Not treated	NA (death from renal failure and pleural effusion)
6547873	62/M	D	–	Headache, splenomegaly	Pancytopenia	Meningeal	Yes	NA	NA	Splenectomy, whole brain radiotherapy, and IT MTX + DXM	PR
1748438	71/M	D	–	Dyspnea, headache, hepatomegaly, splenomegaly	Hyperleucocytosis (323 G/L), anemia, thrombocytopenia	Brain parenchymal (supra-tentorial)	Not tested	CD25+ CD10-	NA	alpha INF	NA (death from leukostasis, intracerebral hemorrhage)
3999626	53/M	R	Splenectomy	Motor ataxia, dizziness, weakness of the left arm.	Pancytopenia	Meningeal	Yes	NA	NA	IT MTX, alpha INF	PR
27116997	59/M	D	–	Headache, dizziness, confusion, slurred speech, frequent falls, facial droop, lymphadenopathy, splenomegaly	Pancytopenia	Meningeal (supra and infra-tentorial)	Yes	CD11c+ CD103+ CD25+	BRAF V600E	IT MTX, systemic Ri + cytarabine (PD), then vemurafenib	CR
36713531	80/M	R	CDA / pentostatin + Ri /CDA + Ri	Fatigue, dizziness, blurry vision and headache, lymphadenopathy, splenomegaly	Hyperleucocytosis (371 G/L), anemia, thrombocytopenia	Brain parenchymal (supra and infra-tentorial)	Not tested	CD11c+ CD25- CD103+ CD10dim CD5+	BRAF V600E	Hydroxyurea and leukapheresis followed by vemurafenib	PR
NA*	68/M	D	–	Acute delusional symptoms	Thrombocytopenia, monocytopenia	Brain parenchymal (infra-tentorial)	No	CD11c+ CD25+ CD103+ CD10- CD5-	NA	CDA	CR

Abbreviations: CDA, cladribine; CR, complete response; CSF, cerebrospinal fluid; D, diagnosis; DXM, dexamethasone; HD, high dose; INF, interferon; IT, intrathecal; M, male; MTX, methotrexate; NA, not available; PD, progressive disease. NA*: KL Chai *et al,* Annals of Clinical Case Reports 2017.; PR, partial response; R, relapse; Ri, rituximab.

We describe here an unusual case of HCL with CNS involvement. Such cases are very rare but treatment with cladribine alone or associated with rituximab leads to impressive responses. Additional work and molecular studies are needed to better understand these unusual HCL presentations.

AUTHOR CONTRIBUTIONS

Fabien Claves, Sylvain Carras, Xavier Troussard, and Lysiane Molina wrote the manuscript. Fabien Claves, Sylvain Carras, Xavier Troussard, Lysiane Molina, Barbara Burroni, Elsa Maitre, and Jean Boutonnat collected biological and clinical data, generated results, and corrected the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING INFORMATION

The study received no funding.

DATA AVAILABILITY STATEMENT

Available from the corresponding author on reasonable request.

ETHICS STATEMENT

The authors have confirmed ethical approval statement is not needed for this submission.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

ORCID

Fabien Claves https://orcid.org/0009-0002-6468-0001
Elsa Maitre https://orcid.org/0000-0002-5967-8225
Xavier Troussard https://orcid.org/0000-0001-6863-9992

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How to cite this article: Claves F, Carras S, Burroni B, Maitre E, Boutonnat J, Troussard X, et al. Atypical meningeal localization of classical hairy cell leukemia with an impressive response to rituximab and cladribine association. A case report and literature review. eJHaem. 2024;5:242–46. https://doi.org/10.1002/jha2.841