Pathology (■ xxxx) **xxx(xxx)**, xxx

CORRESPONDENCE

A rare finding of plasma cell leukaemia with hairy-cell morphology

To the Editor,

Plasma cell leukaemia (PCL) is a very rare and typically highly aggressive type of leukaemia. Prognosis is poor, with median survival below 6 months, and the disease is characterised by peripheral clonal plasmacytosis of peripheral blood ($>2\times10^9$/L PCs or PCs accounting for >20% of nucleated blood cells).[1] Within this rare disease, an even rarer manifestation is the presence of circulating PCs with a villous or 'hairy' lymphocyte morphology. Very few cases of this variant PCL have been described in the literature.[2–11] However, while the available reports do not describe the same parameters [few include karyotype or fluorescence *in situ* hybridisation (FISH) analysis], all of them coincide in the presence of atypical villous cells with a lymphoid appearance that would suggest a chronic B-lymphoproliferative disorder of the hairy-cell type rather than PCL.

Here, we describe the case of a patient with PCL whose PCs had the appearance of villous lymphocytes (hairy plasma cell leukaemia; HPCL) and compare this case with the few cases described in the literature to identify patterns in the laboratory findings.

A 73-year-old woman with a history of osteoporosis treated with calcium, bisphosphonate, and analgesics (paracetamol and ibuprofen) presented at the emergency department with severe asthenia, dyspnoea, back pain, and pain in the right arm after sudden movement. The patient also reported a worsening of her lower back pain during the preceding 6 months. A physical examination revealed mucocutaneous pallor.

A complete patient blood count revealed a leukocyte count of 106×10^9/L containing 86.8% lymphocytes, marked anaemia with a haemoglobin of 54 g/L (reference range 120–160) without reticulocytosis, and a platelet count of 251×10^9/L (130–450). Haemostasis tests revealed no remarkable alterations except for an elevated D-dimer concentration of 3.87 mg/L (<0.5).

Biochemical blood analysis gave results within the reference range for glucose, urea, sodium, potassium and total bilirubin and mildly elevated values for serum creatinine (124 µmol/L, 44–106), urate (0.49 mmol/L, 0.14–0.35), lactate dehydrogenase (392 U/L, 81–234), ALT (45 U/L, <41), and AST (51 U/L, <31).

Given the leukocytosis and anaemia, a peripheral blood smear was performed, revealing small cells with scant basophilic cytoplasm. Most of these cells had small non-polarised cytoplasmic projections (Fig. 1A, green arrows), some had eccentric nuclei (Fig. 1B, red arrow), and a few of them were binucleated (Fig. 1C).

We examined the immunophenotype of peripheral blood due to the signs of chronic lymphoproliferative disorder in the smear test. Initially an eight-colour screening tube was used to rule out clonality and the presence of CD34+ precursors. The tube contained the following antibody combination: kappa FITC, lambda PE, CD34 PerCP-Cy5.5, CD19 PE-Cy, CD10 APC, CD20APC-Cy7, CD45V450/HLA-DR V500. Cells were acquired in a FACSCanto Flow cytometer (BD Biosciences, USA) and analysed with Infinicyt software (Cytognos, Spain).

The flow cytometry study revealed that 83% of total leukocytes consisted of a population with a CD45−, CD34−, CD19−, CD20−, CD10− immunophenotype (Fig. 2A–C). This population was CD66, CD11b and CD33 negative and lacked expression of kappa and lambda surface immunoglobulin light chains, being CD200 positive (data not shown). Because the clonal population did not express CD19 and CD20 with high intensity as hairy cell leukaemia does, CD11c and CD103 were not analysed.

An extension of the study to test for the presence of plasma cells showed that the abnormal cell population was CD38+, CD138+, CD19−, and CD56++, compatible with peripheral plasma cells with an aberrant phenotype (Fig. 2D,E). The population was also positive for lambda clonality of very weak intensity, detected intracellularly (Fig. 2F). The cells were also negative for CD123 and HLA-DR. These findings meet the criteria for plasma cell leukaemia ($>2\times10^9$/L of PCs or >20% of the white blood cell count).

A bone marrow smear revealed hypercellular bone marrow with massive PC infiltration and the presence of plasmablasts. Some of the PCs had hairy cytoplasmic prolongations, while others were binucleated. Flow cytometry immunophenotyping of bone marrow aspirate showed that 85.81% of bone marrow cells were plasma cells (CD38+, CD138+) with an aberrant phenotype similar to that detected in peripheral blood: CD19−, CD56++, CD45−, and with low-intensity lambda light chain restriction detected by intracellular staining.

A conventional cytogenetic study of the BM aspirate revealed normal karyotype cytogenetics (46 XX). FISH detected deletions in chromosome 17p13 (p53) in 43% of cells and in chromosome 13q14 in 68% of cells, the latter involving an IGH-BCL1 rearrangement. Complementary laboratory studies determined total protein (82 g/L, 60–80) and immunoglobulins (IgG 18.9 g/L, 6.5–16; IgM <0.22 g/L, 0.41–2.4; IgA <0.05 g/L, 0.07–0.58). Serum protein electrophoresis detected a gamma monoclonal component at 11.4 g/L. Serum immunofixation identified this component as an IgG lambda+lambda light chain protein with no associated heavy component. The β-2-microglobulin concentration was 10 mg/L (<2), and calcium and albumin were normal. Serum light chain concentrations were 0.32 mg/L for kappa (17–37) and 72.4 mg/L lambda (9–21). In a 24-hour urine sample, the concentration of free lambda light chain (Bence Jones protein) was 6.3 g/24 h (<0.25).

Whole-body computed tomography revealed osteopenia, small lytic lesions in the left scapula, a lytic lesion in the L2 vertebra, and focal hypodense areas in the marrow of the iliac bones and vertebrae.

Print ISSN 0031-3025/Online ISSN 1465-3931

Please cite this article as: Álvarez Flores MB et al., A rare finding of plasma cell leukaemia with hairy-cell morphology, Pathology, https://doi.org/10.1016/j.pathol.2023.07.010

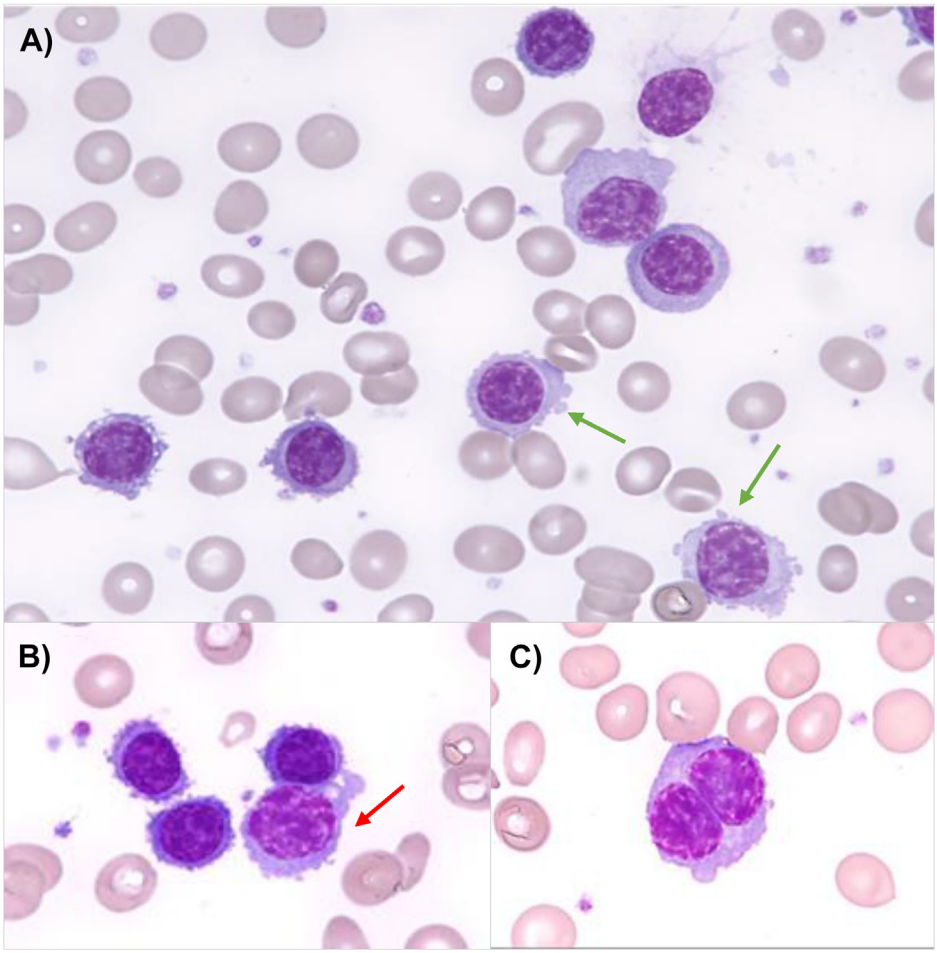

Fig. 1 (A–C) Wright–Giemsa staining of peripheral blood smears, showing atypical cells with a villous, 'hairy-cell' morphology.

The patient refused chemotherapy, transfusion with blood products, and treatment with bortezomib, but accepted dexamethasone and EPO pulses. She had a torpid clinical course, with severe anaemic syndrome, bone pain that was treated with opioid analgesics, and subsequent generalised febrile syndrome. The patient died on day 13 day after admission.

There are very few published reports of PCL with a hairy-cell morphology. All reported cases describe atypical hairy cells with a lymphoid appearance, which would prompt suspicion of chronic B-lymphoproliferative syndrome rather than plasma cell leukaemia in the first instance. Haematologists should be aware of the existence of this variant PCL to avoid delayed diagnosis.

We aimed to compare the patient case presented here with the others described in the literature. However, unfortunately the type of data presented varies between the different descriptions, and this heterogeneity makes it difficult to establish shared patterns that distinguish the presentation of HPCL from that of classical PCL.

Including the patient case presented here, we found 10 case reports of HPCL.[2–11] Of the patients, 60% were male and all had leukocytosis (37.63×10^9/L$\pm$14.49, range 13×10^9/L to 106×10^9/L). In 88.88% of patients, atypical cells with a lymphoid appearance exceeded 40% of all peripheral blood leukocytes. Most patients presented with anaemia (71.40%), elevated serum lactate dehydrogenase (80%), and thrombocytopenia (83.33%). In addition, most patients had renal impairment, with ~80% having serum creatinine above the upper reference limit and a depressed estimated filtration rate (CKD-EPI equation). Uric acid was elevated in all patients, possibly reflecting the haematology-associated increase in nucleic acid production and the depressed renal excretion. The aberrant PC population was CD138+, CD38+, CD19−, and CD45− in all cases (except for one patient with a dim CD45 signal). CD56 expression was detected in 50% of the atypical cell populations. Lambda light chain restriction was detected in 71% of cases (Table 1).

Karyotypes were reported for only three of the patient samples. Although the karyotypes were normal, in all three samples FISH detected alterations in chromosome 13 (monosomy 13 and two deletions in 13q).

The key clinical and cytogenetic differences between primary PCL and multiple myeloma were described by Gundesen *et al.*[12] Given the paucity of data on HPCL, it is difficult to compare the features of classical PCL and HPCL.

This study highlights the limited information available on HPCL and the current inability to determine if its prognosis differs from that of PCL with a classical morphology. It would be interesting to know the incidence of chromosome 13 alterations in HPCL and to define their possible involvement in the development of the disease and responses to treatment for which a larger report of HPCL cases is needed.

Please cite this article as: Álvarez Flores MB et al., A rare finding of plasma cell leukaemia with hairy-cell morphology, Pathology, https://doi.org/10.1016/j.pathol.2023.07.010

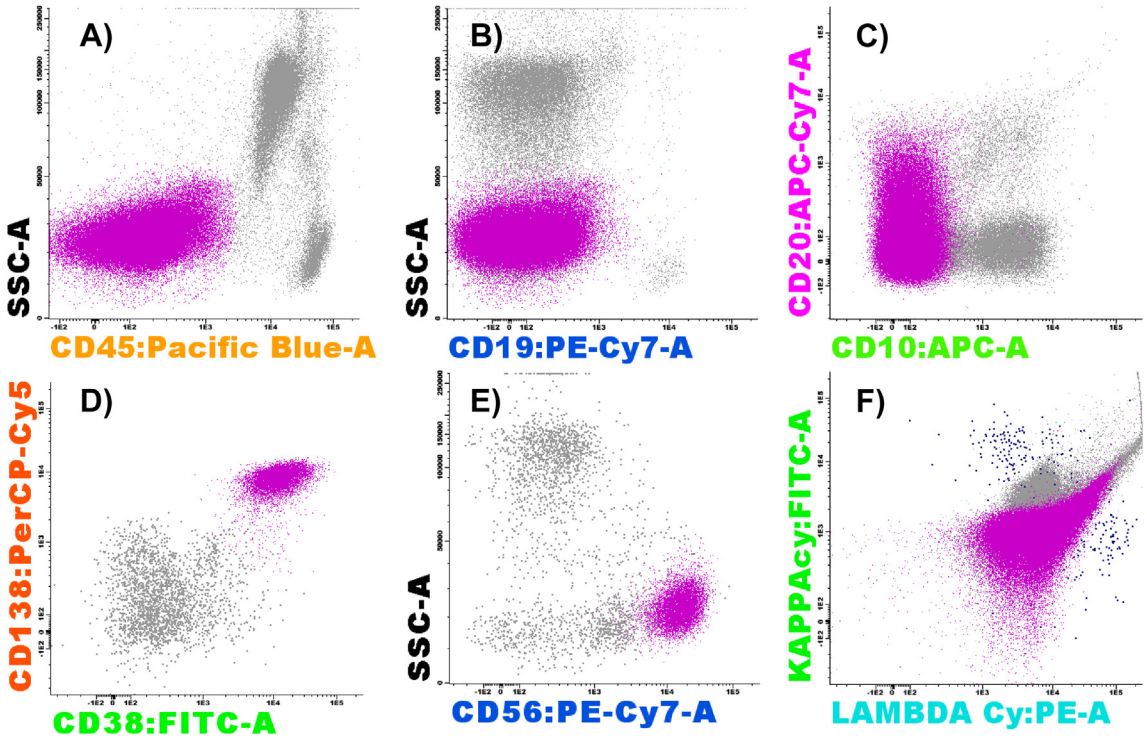

Fig. 2 Peripheral blood immunophenotyping. (A–C) Flow cytometry dot plots revealing abnormal peripheral blood cells (magenta) negative for CD45, CD19, CD20, and CD10. (D,E) Flow cytometry detection of CD38+ and CD138+ clonal plasma cells with aberrant expression of CD56. (F) Intracellular staining revealing lambda light-chain restriction. Polyclonal B lymphocytes are depicted in blue.

Table 1 Flow cytometry immunophenotype, FISH, and karyotype analysis

Authors	Light chain	CD138	CD38	CD19	CD56	CD45	Karyotype	FISH
Alghasham[11]	Lambda	+	+	–	–	ND	46, XX	monosomy 13
Kumar *et al.*[3]	Lambda	+	+	–	–	ND	ND	ND
Li *et al.*[7]	Kappa	+	+	–	+	–	46, XX	13q deletion
Sharma *et al.*[2]	Kappa	+	+	–	–	dim	ND	ND
Tanioka *et al.*[5]	Lambda	ND	+	–	ND	–	ND	ND
Majeed *et al.*[8]	ND	+	+	–	+	–	ND	ND
Álvarez *et al.*	Lambda	+	+	–	+	–	46, XX	del 17p13; del 13q14
Hanbali *et al.*[9]	Lambda	+	+	ND	ND	ND	ND	ND

FISH, fluorescence *in situ* hybridisation; ND, not done.

Acknowledgement: We thank Simon Bartlett for English editing, Marta Morado for her help with the photography of the cytological images and Ataulfo González and Jesús Villarrubia for their morphological consultancy. This research did not require additional funding and was carried out with the resources used for patient diagnosis in the Laboratorio Central de la Comunidad de Madrid, BRSalud.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose. This publication was funded by the CNIC. The CNIC is supported by the Instituto de Salud Carlos III (ISCIII), the Ministerio de Ciencia e Innovación (MCIN) and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (grant CEX2020-001041-S funded by MICIN/AEI/10.13039/501100011033).

María Beatriz Álvarez Flores[1], Marta Jiménez Rolando[2], Nazaret del Amo del Arco[3], Pilar Massó Asensio[4], Raquel Guillén Santos[5], Fernando Cava-Valenciano[5]

[1]Unidad de Citometría de Flujo, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain; [2]Servicio de Hematología, Hospital del Henares, Madrid, Spain; [3]Servicio de Análisis Clínicos, Instituto de Medicina de Laboratorio Hospital Clínico San Carlos, Madrid, Spain; [4]Servicio de Hematología, Hospital Ramón y Cajal, Madrid, Spain; [5]UR Salud, Laboratorio Central de la Comunidad de Madrid, Madrid, Spain

Contact Dr María Beatriz Álvarez Flores.
E-mail: mbalvarez@cnic.es

Please cite this article as: Álvarez Flores MB et al., A rare finding of plasma cell leukaemia with hairy-cell morphology, Pathology, https://doi.org/10.1016/j.pathol.2023.07.010

1. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol* 2003; 121: 749–57.
2. Sharma P, Sachdeva MUS, Ahluwalia J, Malhotra P. Plasma cells with hairy projections and Auer rod-like inclusions in a patient with multiple myeloma. *BMJ Case Rep* 2017; 2017: bcr2017221315.
3. Kumar TN, Krishnamani K, Gandhi LV, Sadashivudu G, Raghunadharao D. Plasma cell leukaemia masquerading as hairy cell leukaemia: a case report. *Indian J Hematol Blood Transfs* 2014; 30: S33–5.
4. Lesesve J-F, Broseus J. Confusing hairy cells in a case of IgG Kappa plasma cell leukemia. *Clin Lab* 2016; 62: 749–50.
5. Tanioka F, Tamashima S, Shimizu S-I, Kobayashi H, Kobayashi Y, Sugimura H. A case of primary plasma cell leukemia with hairy-cell morphology and lambda-type Bence-Jones protein. Immunohistochemical and molecular analysis. *Jpn J Clin Oncol* 2003; 33: 232–7.
6. Lee HJ, Jo D-Y. Plasma cell leukemia with prominent hairy-cell morphology. *Am J Med Sci* 2016; 352: 657.
7. Li T, Zhang Y, Li K, Yang L, Wang Y. Plasma cell leukemia morphologically resembling hairy cell leukemia variant. *Int J Lab Hematol* 2021; 43: 532–3.
8. Memon A, Ali N. Plasma cell leukemia mimicking hairy cell leukemia: extended role of immunophenotyping in correct diagnosis. *J Appl Hematol* 2019; 10: 108–9.
9. Hanbali A, Alrajeh A, Rasheed W. Plasma cell leukemia mimicking hairy cell leukemia. *Hematol Oncol Stem Cell Ther* 2015; 8: 91–2.
10. Bernier GM, Anku V, Graham RC, Johnson CA, Fanger MW. Hairy plasma-cell leukemia. *Blood* 1977; 50: 183.
11. Alghasham N, Rawas W, Owaidah T, Hanbali A. Hairy-plasma cell leukemia. *J Appl Hematol* 2015; 6: 168–71.
12. Gundesen MT, Lund T, Moeller HEH, Abildgaard N. Plasma cell leukemia: definition, presentation, and treatment. *Curr Oncol Rep* 2019; 21: 8.

DOI: https://doi.org/10.1016/j.pathol.2023.07.010

Please cite this article as: Álvarez Flores MB et al., A rare finding of plasma cell leukaemia with hairy-cell morphology, Pathology, https://doi.org/10.1016/j.pathol.2023.07.010