

CASE REPORT

A case of hairy cell leukemia variant

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Abstract

Hairy cell leukemia variant (HCLv) is a rare B-cell chronic lymphoproliferative disorder with features of the classic HCL but presenting some particularities, a poor response to conventional therapy of classic HCL and a more aggressive course of disease with shorter survival than classic HCL. We present a case of a 52-year-old man hospitalized in July 2012 in the Clinic of Hematology of Craiova, Romania, having splenomegaly, leukocytosis with lymphocytosis, anemia and thrombocytopenia, without monocytopenia, which exposed, in the peripheral blood and bone marrow cells, intermediate morphology between hairy cells and prolymphocytes and immunophenotype of mature B-cell phenotype CD19, CD20, CD22, CD11c, CD103, low positive for CD25 and negative for CD3, diagnosed with HCL variant, with no response to conventional chemotherapy and interferon-alpha, an aggressive course of disease and a survival of less than a year from diagnosis.

Keywords: hairy cell leukemia variant, leukocytosis, CD25.

Introduction

Hairy cell leukemia variant (HCLv) is a B-cell disorder, described by Cawley *et al.* in 1980, which accounts for 0.4% of the chronic lymphoid malignancies and 10% of HCL cases, included in the *World Health Organization* (WHO) classification as a provisional entity, affecting elderly or middle-aged males [1, 2]. It has distinct morphological, immunophenotypic and histological features and a more aggressive clinical course than classic HCL. The main features are splenomegaly, leukocytosis, lymphocytosis, anemia and thrombocytopenia without monocytopenia. Morphology of variant cells is intermediate between hairy cells and prolymphocytes, with an unusual large nucleolus relative to their size [3]. The immunophenotype reveals a mature B-cell phenotype CD19, CD20, CD22, CD11c, CD103, FMC7 and surface immunoglobulin, with low or lacking CD25, HC-2 [4, 5]. The bone marrow histology reveals a distinct pattern with interstitial infiltration by lymphoid cells with spaces among them and spleen histology shows an expansion and infiltration of the red pulp of spleen with naked white pulp. Cytogenetic abnormalities are frequent in patients with HCLv: del(17p), +12, and monoallelic p53 are common. The analysis of VH, DH, and JH gene segments of the immunoglobulin gene locus in patients with classic HCL and HCLv revealed that IgH V4-34 rearrangements and unmutated IgH V sequence were highly associated, and IgH V4-34 rearrangements were closely related to the poor prognosis in patients with HCLv [6]. BRAF 600E mutations are absent in HCLv and present at most patients with classic HCL [7–9].

Purine nucleoside analogues (Cladribine and Pentostatin) seem to be less active in HCL variant than classic

HCL, with the addition of monoclonal antibodies (Rituximab) being apparently more effective. Better results have been obtained with anti-CD22-specific immunotoxins, BL22 [10–12]. The course of disease is more aggressive and the survival is inferior in HCL variant than in classic HCL.

The aim of this paper is to present a rare type of B-cell chronic lymphoproliferative disorder, a case of hairy cell leukemia variant, with distinct morphological, immunophenotyping and histological features, a partial response to conventional therapy of classic hairy cell leukemia, a more aggressive clinical course and a shorter survival than classic HCL.

Case report

A 52-year-old man was evaluated in July 2012 in the Clinic of Hematology of Craiova, Romania, for fatigue, fever (38°C) and leukocytosis. At the physical examination, the patient was noted to have splenomegaly and a condensation syndrome at left hemithorax basis. Laboratory results revealed mild anemia with a hemoglobin level 10.4 g/dL, leukocytosis with total white blood count 42 500/mm³ with 87% atypical circulating mononuclear cells, 4% monocytes and 9% granulocytes, thrombocytopenia with a platelet count of 60 000/mm³, erythrocytes sedimentation rate 60/100 mm, fibrinogen 508 mg%, serum lactate dehydrogenase (LDH) 330 U/L. Hepatic and renal tests were normal. A peripheral blood smear revealed numerous circulating mononuclear cells with moderate basophilic cytoplasm with fine circumferential projections, round nuclei and large nucleolus similar to prolymphocytes. Flow cytometry analysis showed B-cells expressing clusters of differentiation CD19, CD20, CD22, CD11c, CD103. The bone marrow biopsy (easy aspirated)

revealed diffuse interstitial infiltration with hairy cells, dislocation of normal hematopoiesis with isolated megakaryocytes (Figures 1–4). Immunohistochemistry of the bone marrow biopsy revealed that infiltrating cells were positive for CD20, DBA-44, partial positive for tartrate-resistant acid phosphatase (TRAP), low positive for CD25 and negative for CD3 (Figures 5 and 6). Thorax X-ray revealed pneumonia of the left inferior lobe. Abdominal CT scan showed homogenous splenomegaly, 15/6 cm (Figure 7). The patient received Cephalosporins 1 g at 12 hours for seven days for bacterial pneumonia with

favorable evolution and then a CVP (Cyclophosphamide + Vincristine + Prednisone) regimen without response. After that, Interferon alpha 3 MIU $\times 3/\text{week}$, s.c., was given, but with no response. The purine nucleoside analogues (Cladribine and Pentostatin) were not available in the clinic and Rituximab is not available for HCL in the national protocol of treatment. The patient refused splenectomy, made frequent complications due to granulocytopenia and thrombocytopenia and died in less than a year from diagnosis from a pulmonary fungal infection.

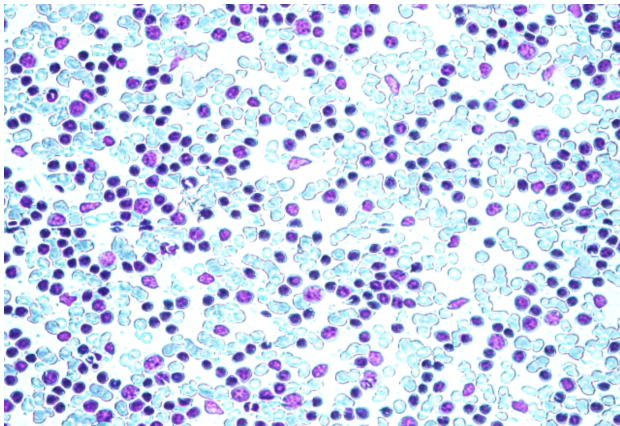


Figure 1 – HCLv peripheral blood. HE staining, $\times 100$.

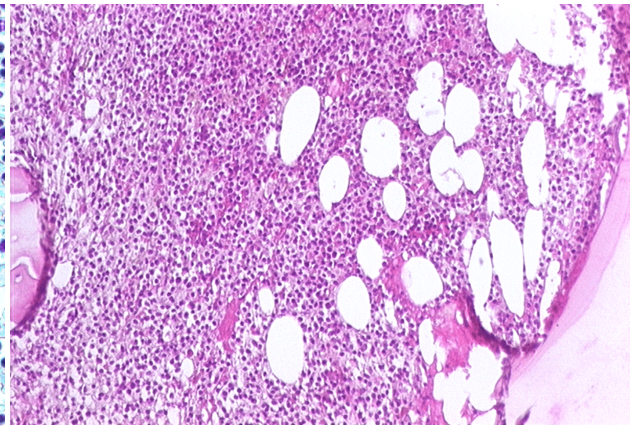


Figure 2 – HCLv: areas with hypercellular bone marrow. HE staining, $\times 100$.

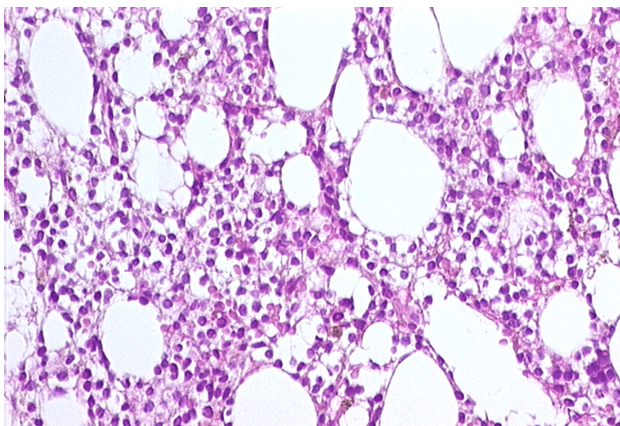


Figure 3 – HCLv: diffuse hairy cells infiltrate. HE staining, $\times 200$.

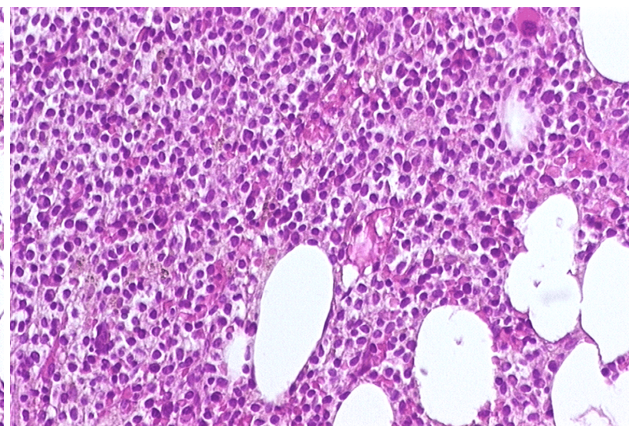


Figure 4 – HCLv: diffuse hairy cell infiltrate, dislocation of normal hematopoiesis, isolated megakaryocytes. HE staining, $\times 200$.

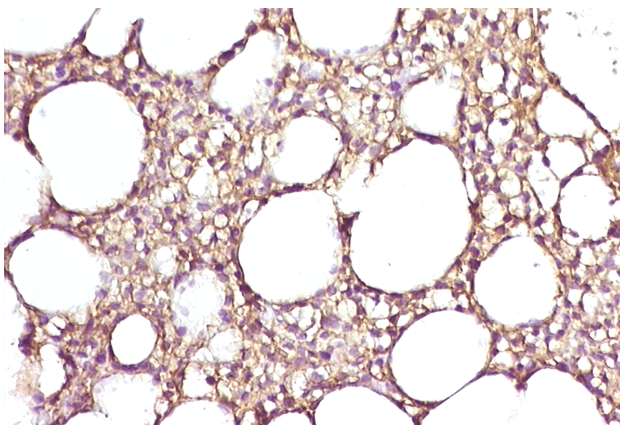


Figure 5 – HCLv: CD20+. Immunostaining for CD20 antibody, $\times 200$.

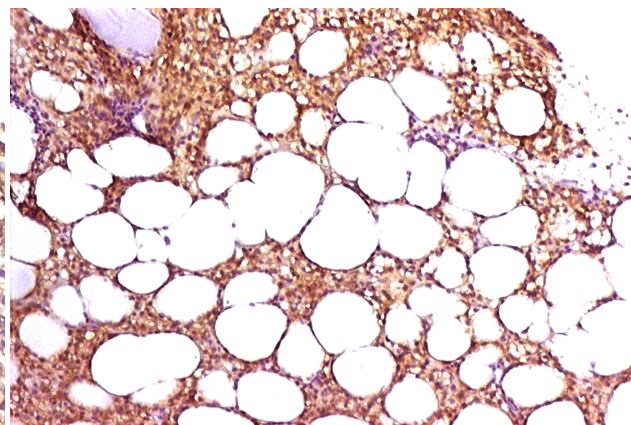


Figure 6 – HCLv: CD25 low positive. Immunostaining for CD25 antibody, $\times 100$.

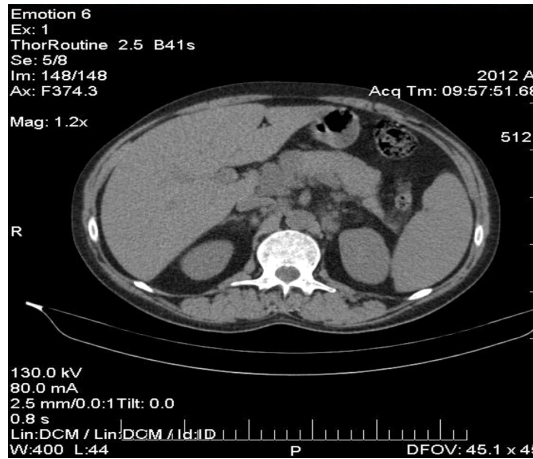


Figure 7 – CT scan: splenomegaly.

Discussion

Based on the splenomegaly, leukocytosis, lymphocytosis and cytopenias without monocytopenia, circulating cells with a morphology intermediate between prolymphocytes and hairy cells and the immunophenotype of a mature B-cell phenotype with expression of the B-cell antigens CD11c and CD103 but low positive for CD25, the patient was diagnosed with hairy cell leukemia variant (HCLv).

According to the new *WHO* classification, HCLv is included as an individual, provisional entity, and a case of HCLv is defined as a B-cell chronic lymphoproliferative disorder with features of classic HCL but some particularities (leukocytosis, presence of monocytes, cells with prominent nucleoli, cells with blastic or convoluted nuclei and/or the absence of circumferential shaggy contours), variant immunophenotype (usually the absence of CD25, annexin-A1, or TRAP), and resistance to conventional HCL therapy [2], frequently involving elderly or middle-aged males (as in our case).

Differential diagnosis was made with classic HCL (splenomegaly, pancytopenia, varying proportions of circulating hairy cells, neutropenia, monocytopenia, bone marrow with a distinct pattern with interstitial infiltration by lymphoid cells with spaces among them, increased reticulin, cells positive for sIg, CD19, CD20, CD22, CD11c, CD25, CD103, FMC7), HCL – Japanese variant (elderly females, important splenomegaly, moderate leukocytosis, less marked hairy projections, a rather round nucleus and weaker positivity for TRAP, immunophenotype positive for sIgG, CD20, CD11c and negative for CD25), B-prolymphocytic leukemia (B-prolymphocytes do not show villous projections and have a less abundant cytoplasm), splenic diffuse red pulp small B-cell lymphoma (leukemic course, with relatively low lymphocytosis, massive splenomegaly, purely diffuse pattern of splenic infiltration by monomorphous small cells with small round nuclei and a pale cytoplasm, intrasinusoidal infiltration of bone marrow, peripheral blood cells of small to medium size with clumped chromatin and round nuclear outline and numerous basophilic villous cytoplasm, immunophenotype positive for CD19, CD20, CD22, CD11c, FMC7 and negative for CD23, BCL6,

annexin A1), mantle-cell lymphoma (splenomegaly, extranodal localization, immunophenotype positive for CD20, CD79a, CD5, CD43, FMC7, cyclin D1 and negative for CD23, CD10, BCL6, presence of t(11;14), splenic marginal zone lymphoma (cells are smaller than HCLv cells, have more condensed chromatin, the cytoplasm is more basophilic and have polar cytoplasmic villi; the bone marrow histology does not show spacing among the cells and instead a predominantly nodular and or intrasinusoidal pattern, immunophenotype is positive for CD20, CD79, sIg, and negative for CD5, CD23, CD10, cyclin D1, cytogenetic exam reveals 7q32-q33, t(2;7), 3+, 5+, 18+).

Various treatment approaches are active in classic HCL: purine nucleoside analogues (Cladribine, Pentostatin), monoclonal antibodies (Rituximab, Alemtuzumab), Interferon alpha, produce partial response or no response in HCLv, and remission is usually shorter than in classic HCL. Patients are resistant to alkylating agents and Interferon alpha and only half achieve partial response to Pentostatin and/or Cladribine. Splenectomy may be a palliative treatment. The monoclonal antibodies (Rituximab and Alemtuzumab) seem to be active in HCLv [13–15]. Currently, immunochemotherapy with Rituximab and purine nucleoside analogues should be considered as the therapy of choice in previously untreated patients. Better results have been obtained with anti-CD22-specific immunotoxins, BL22. A new generation of CD22-specific immunotoxins, Moxetumomab pasudotox (CAT-8015, HA22), highly active in refractory or relapsed classic HCL, also need clinical investigation in HCLv [10].

The course of disease is more aggressive and the survival is inferior in HCL variant than classic HCL. The median survival is of nine years and approximately half of patients die of unrelated causes. Transformation to large cell happens in 6% of patients. The chemotherapy resistance may have a role in the inferior survival in HCLv compared to classic HCL cases [3]. Our patient had a very short survival from diagnosis, correlated with the lack of response to conventional chemotherapy and Interferon alpha.

The originality of the case was represented by the rarity of this type of HCL, difficult differential diagnosis, the lack of response to conventional chemotherapy and Interferon alpha and poor prognosis with aggressive evolution.

Conclusions

Hairy cell leukemia variant is a rare type of B-cell chronic lymphoproliferative disorder characterized by splenomegaly, leukocytosis, lymphocytosis and cytopenia without monocytopenia, circulating cells with a morphology intermediate between prolymphocytes and hairy cells and the immunophenotype of a mature B-cell phenotype with marked expression of the B-cell antigens CD11c, CD103, CD22 and low or lacking CD25, HC2, with partial response to conventional therapy of classic hairy cell leukemia, a more aggressive course of disease and a shorter survival than classic HCL.

Conflict of interests

The authors declare that they have no conflict of interests.

References

- [1] Cawley JC, Burns GF, Hayhoe FGJ. A chronic lymphoproliferative disorder with distinctive features: a distinct variant of hairy-cell leukaemia. *Leuk Res*, 1980, 4(6):547–559.
- [2] Piris MA, Foucar KM, Molejjo M, Campo E, Falini B. Splenic lymphoma/leukemia, unclassifiable. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (eds). *WHO classification of tumours of haematopoietic and lymphoid tissues*. 4th edition, IARC Press, Lyon, 2008, 191–193.
- [3] Matutes E, Wotherspoon A, Catovsky D. The variant form of hairy-cell leukemia. *Best Pract Res Clin Haematol*, 2003, 16(1):41–56.
- [4] Cessna MH, Hartung L, Tripp S, Perkins SL, Bahler DW. Hairy cell leukemia variant. *Am J Clin Pathol*, 2005, 123(1):132–138.
- [5] Matutes E, Morilla R, Owusu-Ankomah K, Houlihan A, Meeus P, Catovsky D. The immunophenotype of hairy cell leukemia (HCL). Proposal for a scoring system to distinguish HCL from B-cell disorders with hairy or villous lymphocytes. *Leuk Lymphoma*, 1994, 14(Suppl 1):57–61.
- [6] Arons E, Suntum T, Stetler-Stevenson M, Kreitman RJ. VH4-34+ hairy cell leukemia, a new variant with poor prognosis despite standard therapy. *Blood*, 2009, 114(21):4687–4695.
- [7] Tiacci E, Trifonov V, Schiavoni G, Holmes A, Kern W, Martelli MP, Pucciarini A, Bigerna B, Pacini R, Wells VA, Sportoletti P, Pettrossi V, Mannucci R, Elliott O, Liso A, Ambrosetti A, Pulsoni A, Forconi F, Trentin L, Semenzato G, Inghirami G, Capponi M, Di Raimondo F, Patti C, Arcaini L, Musto P, Pileri S, Haferlach C, Schnittger S, Pizzolo G, Foà R, Farinelli L, Haferlach T, Pasqualucci L, Rabadan R, Falini B. BRAF mutations in hairy-cell leukemia. *N Engl J Med*, 2011, 364(24):2305–2315.
- [8] Xi L, Arons E, Navarro W, Calvo KR, Stetler-Stevenson M, Raffeld M, Kreitman RJ. Both variant and IGHV4-34-expressing hairy cell leukemia lack the BRAF V600E mutation. *Blood*, 2012, 119(14):3330–3332.
- [9] Tadmor T, Tiacci E, Falini B, Polliack A. The BRAF-V600E mutation in hematological malignancies: a new player in hairy cell leukemia and Langerhans cell histiocytosis. *Leuk Lymphoma*, 2012, 53(12):2339–2340.
- [10] Robak T. Management of hairy cell leukemia variant. *Leuk Lymphoma*, 2011, 52(Suppl 2):53–56.
- [11] Robak T. Hairy-cell leukemia variant: recent view on diagnosis, biology and treatment. *Cancer Treat Rev*, 2011, 37(1):3–10.
- [12] Kreitman RJ, Tallman MS, Coutre S, Robak T, Wilson WH, Stetler-Stevenson M, Noel P, FitzGerald DJ, Buzoianu M, Lechleider R, Kaucic K, Pastan I. Phase I dose-escalation study of CAT-8015 (HA22), a CD22-specific targeted immunotoxin, in relapsed or refractory hairy cell leukemia. *Blood*, 2009, 114:Abstr 888.
- [13] Narat S, Gandia J, Dogan A, Mehta A. Successful treatment of hairy cell leukemia variant with rituximab. *Leuk Lymphoma*, 2005, 46(8):1229–1232.
- [14] Thomas DA, O'Brien S, Bueso-Ramos C, Faderl S, Keating MJ, Giles FJ, Cortes J, Kantarjian HM. Rituximab in relapsed or refractory hairy cell leukemia. *Blood*, 2003, 102(12):3906–3911.
- [15] Găman AM. Hairy cell leukemia – a rare type of leukemia. A retrospective study on 39 patients. *Rom J Morphol Embryol*, 2013, 54(3):575–579.

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