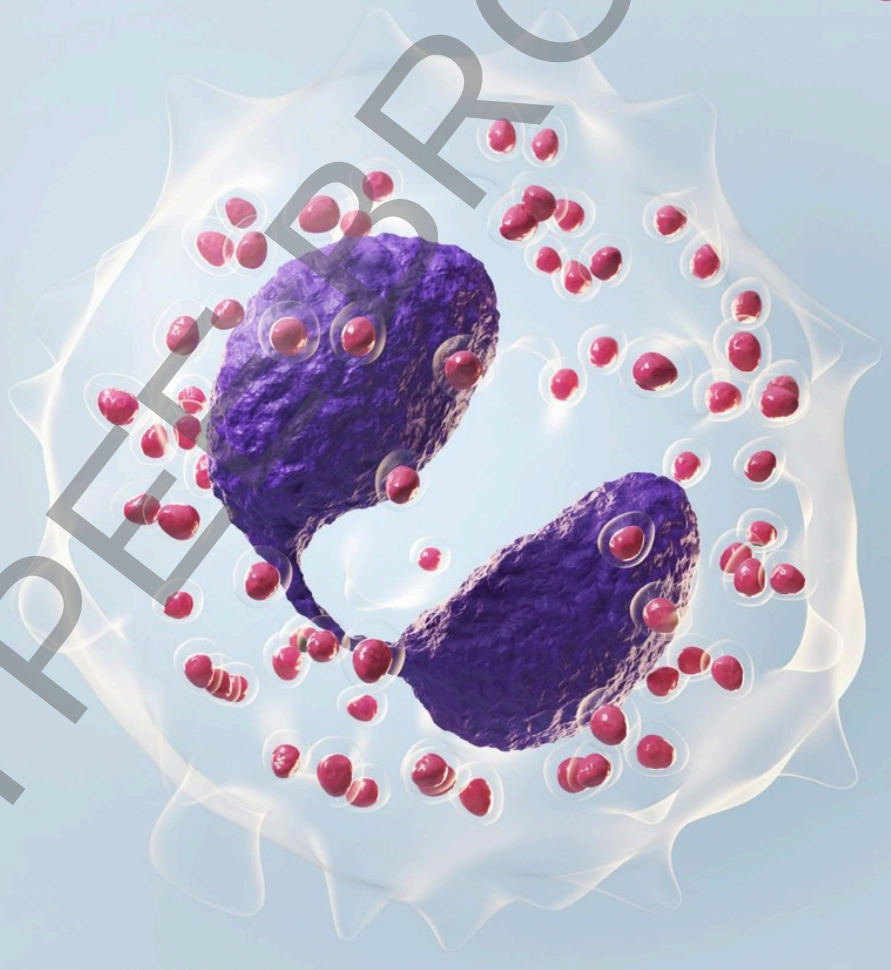
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Postgraduate Review MCQs in HEMATOLOGY

For DM/DNB/FNB/MD/Fellowship Entrance Exams
(Including USMLE, PLAB, NEET, AIIMS, PGIMER and Others)

Editors
Sanjeev Kumar Sharma • Pawan Kumar Singh

4th Edition



Covering

- Clinical Hematology, Medical Oncology, Hematopathology and Transfusion Medicine
- Immunohematology

Foreword
Nitin Gupta

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CHAPTER 33

Hairy Cell Leukemia

1. Most specific marker for the diagnosis of hairy cell leukemia (HCL) is:
a. TRAP
b. DBA 44
c. Annexin A1
d. CD11c

2. Which is the most useful immunohistochemical stain to use when assessing remission status post-treatment in HCL?
a. CD20
b. CD11c
c. CD25
d. CD123
e. Annexin 1

3. Indications for treatment in HCL are:
a. Symptomatic cytopenias
b. Painful splenomegaly
c. Recurrent infections
d. All of the above

4. True regarding treatment for HCL are all, *except*:
a. Cladribine is more efficacious than pentostatin in the treatment of HCL
b. Subcutaneous cladribine administration is likely to be the most cost-effective option
c. Patients who have received cladribine or pentostatin should be transfused only with irradiated blood products
d. Patients who have received cladribine or pentostatin should receive acyclovir and co-trimoxazole prophylaxis

5. Response to purine analog therapy by bone marrow examination should be assessed after:
a. 7 days
b. 28 days
c. 45 days
d. 60 days
e. 120 days

6. Cladribine can be given as:
a. 0.1 mg/kg/day as a continuous IV infusion for 7 days
b. 0.14 mg/kg/day as an IV infusion over 2 hours for 5 consecutive days
c. 0.14 mg/kg/day as an IV infusion once weekly for 6 consecutive weeks
d. 0.14 mg/kg/day as a SC bolus injection for 5 consecutive days
e. All of the above

7. Hairy cell leukemia-variant (HCL-v) differs from HCL by:
a. It is resistant to interferon alpha and rarely responds to cladribine
b. There is lack of monocytopenia and leukocyte count is elevated
c. CD25 and HC2 are not expressed
d. All of the above

8. Patient with hairy cell leukemia can develop:
a. Vasculitis
b. Autoimmune hemolytic anemia
c. Lytic bone disease
d. All of the above

9. True regarding HCL are all, *except*:
a. Male:female ratio is 5:1
b. Median age at diagnosis is 55 years
c. Majority of patients present with pancytopenia
d. Hairy cells are present in nearly all patients
e. All of the above

10. Hairy cell leukemia patient with active infection should be treated with:
a. Cladribine
b. Pentostatin
c. Rituximab
d. Vemurafenib

11. Treatment of variant HCL is:
a. Cladribine
b. Pentostatin
c. Cladribine plus rituximab
d. Vemurafenib

12. True regarding variant HCL is:
a. BRAF V600E negative
b. CD200 negative
c. TRAP negative
d. Annexin 1 negative
e. All of the above

13. True about BRAF V600E mutation in HCL is:
a. BARF mutation can be diagnosed by PCR
b. BARF mutation can be diagnosed by immunohistochemistry
c. Its inhibition can reverse the hairy morphology to normal
d. All of the above

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14. Hairy cell leukemia is treated by:

a. Vemurafenib
b. Dabrafenib
c. Ibrutinib
d. All of the above

15. According to WHO, splenic lymphoma/leukemia includes all, *except*:

a. Hairy cell leukemia
b. Hairy cell leukemia-variant
c. Splenic marginal-zone lymphoma with circulating villous cells
d. Splenic-lymphoma with prominent nucleolus
e. Splenic diffuse red-pulp lymphoma

16. True about hairy cell leukemia includes:

a. Hairy cells secrete fibroblast growth factor 2
b. Hairy cell morphology can be reversed by treatment
c. The absence of *BRAF* mutations is reported in up to 10% of HCL patients
d. All of the above

ANSWERS WITH EXPLANATIONS

1. Ans. c. Annexin A1

Ref: WHO classification of tumors of hematopoietic and lymphoid tissues, Revised Edition.

Annexin A1 is the most specific hairy cell leukemia marker since it is not expressed in any other small B-cell lymphomas other than HCL. Expression of annexin A1 can be used to distinguish HCL from SMZL and HCL variant as both are annexin 1 negative. Despite its specificity, annexin A1 is not useful for detecting minimal involvement at diagnosis or low levels of residual HCL after treatment as it also expressed by myeloid cells and some T cells. Hairy cells are CD5 and CD23 negative, express surface membrane immunoglobulin (SmIg) strongly with either κ (kappa) chain or λ (lambda) chain and are FMC7 positive. Expression of both TRAP and CD72 (the antigen reactive with DBA.44) has been shown to have high sensitivity for HCL and a high specificity for the disease; combined TRAP/DBA.44 positivity was found in only 3% of cases of non-HCL lymphoproliferative diseases. CD11c, CD25 and CD123 also show bright expression. The BRAF V600E mutation is now recognized as the causal genetic event of HCL because it is somatic, present in the entire tumor clone, detectable in almost all cases at diagnosis and stable at relapse.

2. Ans. a. CD20

Ref: Jones G. BCSH Revised Guidelines for the Diagnosis and Management of Hairy Cell Leukaemia and Hairy cell Leukaemia Variant. 2012.

Flow cytometric evaluation should be undertaken when liquid material is available. CD11c, CD25, CD103 and CD123 are advised if HCL is suspected or for monitoring minimal residual disease. Immunohistochemistry on bone marrow trephine specimens should include CD20 and CD72 (DBA.44). Use of DBA.44 and other more HCL-specific antibodies is not recommended unless as part of a wider panel including CD20 since their performance is inferior in MRD detection. Clusters of positively stained cells or widely dispersed CD20-positive lymphocytes are taken as evidence of residual disease. CD20 is the most useful immunohistochemical stain to use when assessing remission status post-treatment.

3. Ans. d. All of the above

Ref: See Q. No. 2; and Grever MR. How I treat hairy cell leukemia. Blood. 2010.

The majority of patients will require therapy to correct the cytopenias and associated problems of anemia, infections, and bleeding. If the patient is asymptomatic and cytopenias are minimal, however, it is reasonable to adopt a watch-and-wait policy. It should be noted that the risk of opportunistic infection in patients with monocytopenia and/or neutropenia is high; even asymptomatic patients may be considered for early treatment.

4. Ans. a. Cladribine is more efficacious than pentostatin in the treatment of HCL

Ref: See Q. No. 2 and 3

Purine analogs (cladribine or pentostatin) are the most appropriate agents for first-line therapy. No difference in efficacy between these has been demonstrated. Subcutaneous cladribine administration is likely to be the most cost-effective option. Patients who have received cladribine or pentostatin should be transfused only with irradiated blood products for the rest of their lives in order to minimize the risk of transfusion-associated graft-versus-host disease. They should also receive acyclovir and co-trimoxazole prophylaxis for herpes infections and *Pneumocystis jiroveci* infection respectively until the lymphocyte count is $\geq 1 \times 10^9$/L. In administering either pentostatin or cladribine, careful attention should be directed to renal function, as these agents are excreted through a renal route. Some prefer to use pentostatin because it permits titration of dose and schedule, cladribine has generally been regarded as the treatment of choice, with pentostatin being recommended for those in relapse.

5. Ans. e. 120 days

Ref: Jones G, Parry-Jones N, Wilkins B, Else M, Catovsky D. BCSH Revised Guidelines for the Diagnosis and Management of Hairy Cell Leukaemia and Hairy cell Leukaemia Variant. Br J Haematol. 2012;156(2):186-95.

Response to purine analog therapy should be assessed by bone marrow examination once the blood count has recovered, typically 4–6 months after cladribine therapy

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or after 8–9 courses of pentostatin. Eradication of minimal residual disease (MRD), in contrast to overtly persistent disease, should not be the aim of therapy except as part of a clinical trial. CR is defined as the absence of hairy cells from the peripheral blood and bone marrow along with resolution of organomegaly and cytopenias. In CR, immunohistochemistry reveals no clustering (≥3 cells) of CD20-positive or DBA.44-positive cells.

6. Ans. e. All of the above

Ref: Grever MR. How I treat hairy cell leukemia. Blood. 2010;115(1):21-8.

Cladribine can be given with either of the routes and dosages. The experience from Scripps Clinic with a 7-day administration of this agent at 0.1 mg/kg per day by continuous intravenous infusion showed that 91% of patients achieved a complete remission. If the agent is administered at 0.14 mg/kg per day by a 1- or 2-hour intravenous infusion for 5 doses, the results are reported to be similar. Subcutaneous administration for 5 or 7 days or weekly administration by intravenous route for 5 or 6 weeks produces comparable rates of complete remission.

7. Ans. d. All of the above *Ref: See Q. No. 2 and 3*

Hairy cell leukemia-variant is considered different from HCL and is categorized separately in the WHO classification. It also responds differently to standard HCL treatment, being generally resistant to interferon alpha and rarely achieving complete response with either pentostatin or cladribine. HCL-variant differs from HCL in the lack of monocytopenia and the elevated white blood cell count, in the region of 40–60 $\times 10^9$/L. Cells in most cases of HCL-v are villous and large, as in HCL, but have a distinct nucleolus and round nucleus resembling B-cell prolymphocytic leukemia (B-PLL). Bone marrow is often easy to aspirate in HCL-v because the reticulin fiber content is low. The immunophenotype of HCL-v cells differs from that of HCL in that Annexin 1, CD25 and HC2 are not expressed. CD103 is expressed infrequently and CD11c is nearly always positive. There is no adequate treatment for this condition. Splenectomy has shown good partial remission in two-thirds patients. Purine analogs combined with rituximab have also been used.

8. Ans. d. All of the above

Patients with HCL may develop disease-related autoimmune complications, including vasculitis and autoimmune hemolytic anemia. Lytic bone disease has also been observed, and extramedullary HCL has involved many tissues within the body.

9. Ans. d. Hairy cells are present in nearly all patients

Ref: Troussard X. Hairy cell leukemia 2018: update on diagnosis, risk-stratification, and treatment. Am J Hematol. 2017;92:1382-90.

Hairy cell leukemia has a striking male predominance, with a male:female ratio of approximately 5:1. The median age at diagnosis is approximately 50–60 years. The majority of patients present with pancytopenia. Monocytopenia is characteristic. Circulating hairy cells in the blood are generally sparse and may be absent.

10. Ans. d. Vemurafenib

Ref: Tiacci E. Targeting mutant BRAF with vemurafenib in relapsed or refractory hairy cell leukemia. NEJM. 2015;373:1733-47.

One of the most challenging clinical situations involves the patient with HCL who requires treatment but has an active infection. Attempts to control the infection should be pursued before beginning treatment with the purine nucleoside analog. Vemurafenib has no myelotoxicity. Vemurafenib increases peripheral blood counts and thus enhances the control of infection. Both cladribine and pentostatin cause profound and prolonged T-cell depletion and increase the risk of infections.

11. Ans. c. Cladribine plus rituximab

Ref: Thompson PA. How I manage patients with hairy cell leukemia. Br J Haematol. 2017;177:543-56.

Hairy cell leukemia variant responds poorly to cladribine monotherapy. It also responds poorly to therapy with pentostatin. The combination of cladribine and rituximab achieves the maximum response in HCL variant. It is BARF negative so BARF inhibitor vemurafenib is not effective. Patients with multiply relapsed HCL variant are appropriate candidates for moxetumomab pasudotox because HCL variant retains a high level of expression of CD22, and bendamustine with rituximab or pentostatin is also appropriate for HCL variant.

12. Ans. e. All of the above

Ref: Troussard X. Hairy cell leukemia 2018: update on diagnosis, risk-stratification, and treatment. Am J Hematol. 2017;92:1382-90.

A more aggressive variant of HCL lacking CD25, Annexin 1, TRAP, and BRAF V600E, called HCL variant, has been classified as a separate disease by the WHO. HCL variant has more lymphocytosis and less severe cytopenias compared with classic HCL. BRAF V600E mutation is considered as the molecular hallmark of the classic HCL.

13. Ans. d. All of the above

Ref: Falini B. BRAF V600E mutation in hairy cell leukemia: from bench to bedside. Blood. 2016;128(15):1918-27.

The BRAF V600E mutation causes constitutive activation of the RAS-RAF-MEK-ERK signaling pathway leading to HCL. The BRAF V600E mutation can be detected in BM or peripheral blood samples by Sanger sequencing or other more sensitive polymerase chain reaction (PCR)-based techniques. An alternative approach for detecting BRAF V600E in routine paraffin sections is based on

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immunostaining with the monoclonal antibody (VE1) specifically directed against the BRAF V600E mutant. This antibody has the potential to represent a reliable surrogate for molecular PCR assays. BRAF inhibition dramatically reversed the characteristic phenotypic and molecular signature of classic HCL cells. These changes coincided with loss of the hairy cytoplasmic projections seen by light microscopy. Subsequently, cells undergo apoptosis. So, exposure of primary HCL cells to BRAF and MEK inhibitors result in conversion of their morphology from "hairy" to "smooth".

14. Ans. d. All of the above

Newer hairy cell leukemia (HCL) treatments focus on targeted therapies such as BRAF inhibitors (vemurafenib and dabrafenib) and BTK inhibitors (ibrutinib), often combined with anti-CD20 antibodies such as rituximab, offering alternatives to standard purine analogs (cladribine/pentostatin) for relapsed or frail patients.

15. Ans. b. Hairy cell leukemia-variant

The World Health Organization (WHO) has classified splenic lymphoma/leukemia into four different types: (1) hairy cell leukemia (HCL), (2) splenic marginal zone lymphoma (SMZL), with circulating villous cells in the peripheral blood, (3) splenic lymphoma with prominent nucleolus (SLPN) and, (4) splenic diffuse red pulp lymphoma (SDRPL). The term of SLPN has replaced the previous entity—variant form of HCL (HCL-V) and CD5 negative B pro-lymphocytic leukemia (B-PLL).

16. Ans. d. All of the above

Ref: Troussard X, et al. Hairy cell leukemia: Update on diagnosis, risk-stratification, and treatment—Annual updates in hematological malignancies. Am J Hematol. 2024;99:679-696

Hairy cell leukemia is characterized by BM fibrosis, leading to dry tap when performing BM aspiration. This fibrosis is due to secretion of fibroblast growth factor 2 (FGF-2), and transforming growth factor beta 1 (TGF-β1) by malignant hairy cells. In vitro exposure of primary HCL cells to BRAF inhibitors and MEK inhibitors can induce dephosphorylation of MEK/ERK, thereby causing loss of the HCL-specific genes, reversion of the morphology of hairy cells to smooth surface cells, and then induction of apoptosis.

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- The book has been divided into various sections and the questions have been answered and explained in detail with references. There is a self-assessment section followed by tables for quick revision in the end.

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