Extranodal NK/T Cell Lymphoma of the Jejunum Complicated by Hemophagocytic Syndrome: Practical Problems Encountered by a Pathologist

Jinkala Sree Rekha · Rakhee Kar · Sajini Elizabeth Jacob ·
Neelaiah Siddaraju · Bettadpura Shamana Suryanarayana ·
Molly Mary Thabah · Rakesh Naik · Nanda Kishore Maraju

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Abstract Extranodal NK/Tcell lymphomas (ENKTL) are rare, aggressive lymphomas. The most common primary site of involvement is the nasal cavity, nasopharynx and paranasal sinuses. The other sites of primary involvement are skin, gastrointestinal tract and testis. Advanced disease can show lymph node, bone marrow and peripheral blood involvement. We report a case of ENKTL of the jejunum, showing peripheral pancytopenia and haemophagocytosis in the bone marrow. The intestine showed multiple intestinal perforations, with evidence of infiltration by lymphoma with coexistent strongyloides infestation. The patient showed disseminated disease in the form of

lymphadenopathy and had a rapidly downhill course and expired on 5th day of admission. We also discuss the problems encountered by the pathologist in diagnosing these uncommon lymphomas.

Keywords Extranodal NK/Tcell lymphomas (ENKTL) · Haemophagocytosis

Introduction

Primary gastrointestinal (GI) tract lymphomas account for 30–40 % of extranodal lymphomas and comprise 10–15 % of all non-Hodgkin lymphomas [1]. Stomach is involved in about 60–75 % of the cases, followed by the ileum, caecum, colon and rectum [2]. B cell GI lymphomas are relatively more common than the T cell variants. Extranodal NK/T cell lymphoma (ENKTL) is a very rare aggressive lymphoma occurring primarily in the nasal cavity, nasopharynx and paranasal sinuses but also involves a number of extranasal locations including the GI tract. We report an unusual case of ENKTL of the jejunum clinically masquerading as hemophagocytic syndrome.

Case Report

A 21 year old lady presented to our emergency department with history of high grade fever for 20 days, abdominal pain for 15 days, vomiting and bloody diarrhoea for 5 days prior to presentation. There was no significant past medical history.

On examination the patient was conscious, alert and febrile. She was tachypneic with respiratory rate of 44/min, her pulse rate was 130/min and blood pressure of

J. S. Rekha · R. Kar (✉) · S. E. Jacob · N. Siddaraju
Department of Pathology, Jawaharlal Institute of Postgraduate
Medical Education and Research, Puducherry 605006, India
e-mail: rakhee_kar@rediffmail.com; drrakheekar@gmail.com

J. S. Rekha
e-mail: sree.path177@gmail.com

S. E. Jacob
e-mail: jacobsajini6@gmail.com

N. Siddaraju
e-mail: rajusiddaraju@gmail.com

B. S. Suryanarayana · M. M. Thabah · R. Naik
Department of Medicine, Jawaharlal Institute of Postgraduate
Medical Education and Research, Puducherry 605006, India
e-mail: sujukumi@gmail.com

M. M. Thabah
e-mail: mthabah@yahoo.com

R. Naik
e-mail: rakeshbmc@gmail.com

N. K. Maraju
Department of Surgery, Jawaharlal Institute of Postgraduate
Medical Education and Research, Puducherry 605006, India
e-mail: nkmaraju@gmail.com

Fig. 1 **a** Bone marrow aspirate showing evidence of haemophagocytosis (Giemsa $\times 400$); *inset* showing a macrophage with phagocytosed erythroid precursors (Giemsa $\times 1,000$). **b** FNAC of the cervical lymph node showing atypical large lymphoid cells (Giemsa $\times 400$); *inset* showing a macrophage with hemophagocytosis (Giemsa $\times 1,000$)

100/60 mmHg. She had mild pallor and icterus, bilateral pedal edema. Bilateral cervical and axillary lymph nodes were enlarged. Abdominal examination revealed diffuse tenderness with moderate splenomegaly and absent bowel sounds. Other systems were normal on examination.

Baseline hemogram showed pancytopenia with Hb-6.4 g/dl, TLC-3,200/cumm (DLC-N70 L25) and platelet count-26,000/cumm. The liver function tests were altered. Kidney functions tests were normal. Patient was started on oxygen by mask and intravenous antibiotics were given after taking blood and urine cultures. Plain chest radiograph was normal.

As patient had fever, splenomegaly, and pancytopenia, work up for haemophagocytosis was done. Bone marrow aspirate showed features of haemophagocytosis (Fig. 1a). Fine needle aspiration cytology of the cervical lymph node showed atypical large lymphoid cells and macrophages with hemophagocytosis (Fig. 1b). A biopsy of the cervical lymph node could not be done immediately because of thrombocytopenia. Serum ferritin was 8,000 mg/dl, serum triglycerides was 431 mg/dl. ANA by immunofluorescence was negative. Echocardiography showed a normal LV function and there were no vegetations. Serum EBV capsular antigen was negative. The serology for typhoid, dengue, leptospira, rickettsial infection were negative. Patient was started on IVIG for the hemophagocytosis under antibiotic cover. By the third day after admission, patient started deteriorating rapidly and required mechanical ventilation for acute lung injury. Abdominal signs of peritonitis appeared and X-ray showed free gas under the diaphragm. CECT of abdomen suggested small bowel

perforation and the patient was taken up for emergency laparotomy. Intra-operatively entire small bowel appeared unhealthy with about 16 perforations at different sites in the small bowel. Limited resection and exteriorisation of the bowel was done. The patient continued to remain on a downward course, developed refractory shock, multiorgan failure and expired on the 5th day of admission.

The jejunal resection specimen sent for histopathological examination showed multiple transmural perforations (Fig. 2a). There was a transmural infiltration of the bowel wall by atypical lymphoid cells. These cells were large with moderate amount of pale eosinophilic cytoplasm, round to oval elongated vesicular nuclei, with irregular, convoluted nuclear contour and inconspicuous nucleoli (Fig. 2b). Angiocentricity of the tumor cells was appreciated (Fig. 2c). The adjacent intestine did not show evidence of villous atrophy, crypt hyperplasia and increase in intraepithelial lymphocytes. In addition the adjacent intestinal segment showed infestation by adult worms of helminthic parasite, morphologically strongyloides (Fig. 2d). The atypical lymphoid cells were CD3 and CD56 positive; CD4, CD8, CD5 and CD2 were negative. CD7 and CD30 were focally positive. Ki67 labelling index was 40 %. CD68 highlighted the interspersed histiocytes. IHC with EBV-LMP1 was negative. Though CD2 and EBV-LMP1(IHC) was negative, taking the morphological features along with CD3 and CD56 positivity and the aggressive clinical behaviour into consideration, a diagnosis of ENKTL of the jejunum with infestation by strongyloides complicated by hemophagocytosis of the bone marrow was given. We could not do in situ

Fig. 2 Jejunal resection specimen showing **a** transmurial intestinal perforation (H&E $\times 20$); **b** transmurial infiltration of the bowel wall by atypical lymphoid cells (H&E $\times 100$); **c** angiocentricity of the atypical lymphoid cells which are large with moderate amount of pale eosinophilic cytoplasm, round to oval elongated vesicular nuclei, with

irregular, convoluted nuclear contour and inconspicuous nucleoli (H&E $\times 400$); **d** adjacent intestinal segment showing infestation by adult worms of helminthic parasite, morphologically strongyloides (H&E $\times 400$)

hybridisation for EBER (EBER-ISH) in our institute as it was not available.

Discussion

NK/T cell lymphomas are extremely rare. Extranodal NK/T cell lymphomas (ENKTL) are aggressive and are exclusively seen extranodally. The most common primary site of involvement is the nasal cavity, nasopharynx and paranasal sinuses. The other sites of primary involvement are skin, gastrointestinal tract and testis. Disseminated disease can show lymphnode involvement secondarily [3].

The primary intestinal NK/T cell lymphomas usually present with complaints of bleeding abdominal pain and epigastric soreness. Endoscopically they are characterized by superficial/erosive, ulcerative, or ulceroinfiltrative lesions without fungating mass [4]. Usually they present at an advanced stage of disease with involvement of multiple extranodal sites. Our case also presented with melena, multiple intestinal perforations and an advanced stage of

the disease. There are case reports where this involvement was misdiagnosed as enteritis and tuberculous peritonitis [5, 6].

In a case like ours, the other differential entities like peripheral T cell lymphoma, NOS (PTCL-NOS) and Enteropathy associated T-cell lymphoma (ETL) were considered. PTCL-NOS is extremely uncommon in the GIT, and presents with non-specific complaints [7]. They are usually CD3+, CD4+, CD8– or CD4– CD8–. ETL was less likely as the adjacent intestinal segment did not show evidence of villous atrophy or increased intraepithelial lymphocytes. The features other than morphology and immunohistochemistry which went in favour of ENKTL in our case are the presence of multiple intestinal perforations, large areas of necrosis, angiocentricity of the tumor cells, lymphnode involvement and the aggressive clinical course.

Three major categories of extranodal T/NK cell tumors are recognized by WHO (1) nasal (2) intestinal and (3) subcutaneous panniculitis-like depending on their sites of involvement [8]. The immunophenotypic features

of ENKTL are variable. They are characterized by CD2+, CD56+, membranous CD3–, cytoplasmic CD3+. Cytotoxic molecules such as granzyme, perforin, TIA 1 are also positive; negative for other T or NK cell markers such as CD4, CD5, CD8, TCR δ , β F1, CD16 and CD57. Occasionally CD7 and CD30 are positive [3]. In a study done by Schwartz et al. [9] CD2 positivity was seen in 93 % of cases. If immunohistochemistry alone is used, it is difficult to establish the clonality and differentiate ENKTL from other PTCL [10]. The atypical lymphoid cells in the present case were CD3 and CD56 positive; CD4, CD8, CD5 and CD2 were negative. CD7 and CD30 were focally positive. In our institute polyclonal CD3 is used which cannot distinguish between surface and cytoplasmic CD3 positivity. Li et al. [11] in his study, describes two lineages of ENKTL, NK cell and T cell lineages. NK-cell lineage, being cytoplasmic CD3+, CD4–, CD5–, CD56+ and/or no evidence of monoclonal T-cell receptor-gamma rearrangements. T-cell lineage which are surface CD3+, CD4+, CD5+, or had monoclonal T-cell receptor gamma rearrangements. Taking this into consideration our case is more likely to be of NK-cell lineage. However, EBV shows a very strong association with ENKTL in both the NK cell as well as the T cell lineage. EBER-ISH is the reliable method of demonstrating EBV association which could not be done in our case. However, there are studies in the literature that say that the association seems site dependent and shows some geographic variation [8].

ENKTL are known to present with advanced disease and multiple extranodal involvement. In the advanced stages, these patients show features of hemophagocytosis and manifest with pancytopenia. The distinction between haemophagocytosis and lymphomatous infiltration as a cause of the pancytopenia might not be easy. Haemophagocytosis occurs commonly in the liver, spleen, and bone marrow in NK cell lymphomas. It may be reactive, and is itself not necessarily an indicator of infiltration in the involved tissue [12]. In our case, the bone marrow aspirate showed convincing evidence of haemophagocytosis; no atypical cells were seen on the aspirate. The trephine biopsy however showed few interstitial CD3 positive which were negative for CD56, CD2, EBV-LMP1 and hence could not be taken as bone marrow involvement. Studies show that bone marrow biopsy may show patchy and inconspicuous involvement by NK/T cells [12]. These cells may or may not be positive for CD56 and so if these cells are positive for EBER, then only the marrow is considered to be definitely involved by the lymphoma. EBER-ISH has been shown to be more sensitive than CD56 immunostaining in detecting occult bone marrow infiltration by NK cell lymphoma [12].

ENKTL are known to occur in the setting of immunosuppression. In our patient there was no serological or

clinical evidence of immunosuppression. Another interesting feature in our case was severe intestinal strongyloidosis. Wang et al. [13] reported a case of extranodal Nasal NK/Tcell lymphoma with duodenal strongyloidosis; this patient also did not have any evidence of immunosuppression as in our case. We attribute the cervical lymphnode involvement as a part of the dissemination of the disease. Li et al. [11] has described lymphadenopathy in 20 % of patients in their study.

Conclusion

This report describes a rare case of jejunal ENKTL with coexistent strongyloides infestation presenting with disseminated disease, intestinal perforation and features of hemophagocytic syndrome. It highlights the aggressive behavior of these neoplasms and discusses the practical problems faced by a pathologist in diagnosing these neoplasms in a resource limited setting. A complete workup with a combination of clinical, morphological and immunophenotypic features coupled with molecular genetic studies where available is necessary to characterize these neoplasms.

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