Cavitating Mesenteric Lymph Node Syndrome and Enteropathy-Associated T Cell Lymphoma as First Manifestation of Celiac Disease

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About the Authors

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Summary

Celiac disease (CD) is a common systemic disease, affecting about 1.0% of the population. Classical presentation includes malabsorption syndrome and deficiencies of macro-/micronutrients. Patients with undiagnosed CD may be referred to hematologists with different hematologic issues, including anemia, thrombocytosis, thrombocytopenia, leukopenia, venous thromboembolism, hyposplenism, and IgA deficiency. CD imposes an increased risk of various lymphomas, especially intestinal T- and B-cell lymphomas. Enteropathy-associated T-cell lymphoma (EATL) is a rare and aggressive disease with poor prognosis and often fatal complications. Here we present a case of EATL associated with cavitating mesenteric lymph node syndrome as a first manifestation of undiagnosed CD.

Résumé

La maladie coeliaque (MC) est une maladie systémique que l'on rencontre fréquemment et qui touche 1,0 % de la population. Ses manifestations classiques comprennent le syndrome de malabsorption et certaines carences en micro/macronutriments. Les patients chez qui la maladie n'a pas été diagnostiquée sont parfois adressés à un hémатologue pour divers problèmes hématologiques, comme de l'anémie, une thrombocytose, une thrombocytopénie, une leucopénie, une thromboembolie veineuse, un hyposplénisme et une carence en IgA. La MC entraîne un risque accru de divers lymphomes, en particulier des lymphomes T et des lymphomes malins à cellules B de l'intestin. L'entéropathie associée au lymphome T (EALT) est une maladie rare et agressive, à pronostic sombre et dont les complications sont souvent fatales. Nous présentons ici un cas d'EALT associé à un syndrome de ganglions mésentériques avec formation de cavernes en tant que première manifestation d'une MC non diagnostiquée.

Case

A 71-year old South American woman was referred for a suspected diagnosis of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). She had an over 20-year history of intermittent abdominal discomfort and noticed progressive symptoms over the last 3 years. Three months prior to the visit, the patient developed fatigue, night sweats, anorexia, increasing abdominal girth, heartburn, abdominal pain with intermittent diarrhea, and weight loss. She denied lymphadenopathy, skin rash, fever, or cough. There was no history of travel and consumption of unusual or uncooked food. Her medical history was significant for osteoarthritis, hypertension (currently controlled on Propranolol, 40 mg daily). She was a lifelong non-smoker and occasional ethanol consumer with an unremarkable family history. She denied any hepatitis or human immunodeficiency virus (HIV) risk factors. Physical exam was unremarkable, except for soft and distended abdomen with tenderness on palpation.

Investigations showed mild macrocytic anemia (hemoglobin = 114 g/L, mean corpuscular volume = 100.2) and

leukopenia (white blood cells [WBCs] = $3.9 \times 10^9/L$). Platelet count was normal ($237 \times 10^9/L$) and chemistry was normal except for an elevated lactate dehydrogenase [LDH] ($259 U/L$, $N \leq 220$). Computed tomography (CT) of the thorax was clear, but abdomen/pelvis CT revealed numerous multiple rim-enhancing hypoattenuating cystic-like round lesions within the jejunal mesentery and left paraaortic areas, suspicious for multiple necrotic lymphadenopathy (Figure 1). The largest of them was 4.6×3.8 cm. Repeated CT noticed overall interval increase in size of most of these lesions and reported them as possible cavitory mesenteric lymph node syndrome. Mesenteric fine needle biopsy aspiration yielded chylous milky fluid, associated with collapse of the cyst (Figure 2A). There was no solid component suitable for the core biopsy, and clinically the lymph nodes were not amenable to surgical excisional biopsy. Available material yielded malignant-looking lymphocytes, with atypical enlarged convoluted nuclei and deeply basophilic cytoplasm.

Flow cytometry identified population of T-cells positive for markers CD2 and CD7, negative for CD3, CD4, CD5, and CD8. Further work up for cystic findings in the mesentery was negative for HIV 1 and 2, Epstein-Barr virus (EBV), hepatitis B, Echinococcus, and Schistosoma. Bone marrow aspiration showed mild T-cell lymphocytosis, with a subpopulation of small- to medium-sized T-cells, with the same immunophenotype, consistent with T-cell lymphoproliferative

Figure 1. CT abdomen. Note multiple large rim-enhancing hypoattenuating cystic-like round lesions (arrows), borderline representing cavitating lymph nodes.

Figure 2A. The material aspirated from the mesenteric cysts showed the characteristic cream-like appearance of chyle.

Figure 2B. High power examination of the duodenal biopsy shows infiltration of lamina propria with intraepithelial lymphocytes. Occasional cells showing marked atypia (arrow). Inset: Low power, showing loss of villous architecture with flat mucosal surface.

disorder. Based on clinical and laboratory data, we diagnosed her with enteropathy-associated T-cell lymphoma (EATL) type I in association with cavitating mesenteric lymph node syndrome.

At that time we raised the possibility of celiac disease (CD). Her gliadin antibody IgG was 110 units, Ig A was 390 units, tissue transglutaminase IgG was less than 4 units, and tissue transglutaminase IgA was 290 units (our laboratory ranges are negative as < 20, weakly positive as 20–30, and positive as > 30 units). To confirm the diagnosis of celiac disease, an esophagogastroduodenoscopy was performed. Duodenal biopsy showed severe mucosal flattening, villous atrophy with loss of architecture, and intraepithelial infiltrate with atypical T-cells, consistent with EATL on a background of CD (Figure 2B). Within one week of starting a gluten-free diet, the patient noticed improvement in gastrointestinal symptoms. She has since started CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) chemotherapy for the management of her Stage 4B EATL. Initially she responded to chemotherapy and achieved partial response, however tumor progressed and the patient was taken off active treatment.

Discussion

The natural history of CD varies widely among patients. The usual sequence of events is the following: 1) serological appearance of celiac-specific antibodies, 2) development of intestinal enteropathy, 3) onset of symptoms, 4) progression to complications. However, not all the events may occur. The duration of each phase can range from weeks to decades.¹

Frequent manifestations, presenting in 40–50% of patients with CD, are chronic diarrhea, weight loss, and abdominal distention. Other presentations include isolated iron deficiency with or without anemia, recurrent abdominal pain, aphthous stomatitis, high level of aminotransferases, chronic fatigue, and reduced bone mineral density.²

CD is a common cause of various hematologic disorders. Anemia is the most common presentation of CD and is most frequently found in patients with undiagnosed or untreated CD. Anemia in CD is usually hypoproliferative, secondary to impaired absorption of essential nutrients, as follows: iron, folate, B12, and less frequently copper, B6, pantothenic acid, and riboflavin. Thrombocytosis occurs in up to 60% with CD.

On the other side, patients with CD may develop thrombocytopenia. CD is also associated with both increased venous thromboembolism, which may be the presenting feature, and abnormalities in coagulation factors (e.g., vitamin K), resulting in an abnormal bleeding tendency. Other manifestations include hyposplenism with Howell-Jolly bodies in peripheral blood film and IgA deficiency.

Development of intestinal lymphoma is well described and is possibly a major contributor to mortality in patients with CD. The risk is highest for intestinal EATL, which is a rare primary extranodal and aggressive malignancy with an incidence of less than 1% of all non-Hodgkin's lymphomas. EATL is usually associated with refractory CD, EATL type I. This type frequently has large-cell or pleomorphic cytology with various, abnormal, multinucleated forms and is usually CD56 negative.³ It has a poor prognosis, whether it occurs de novo or results from long-term untreated refractory CD. The largest reported series in the literature showed a 1-year survival of only 31% and 5-year survival of 11%.⁴

Cavitating mesenteric lymph node syndrome (CMLNS) is a rare complication of CD. A paper by McBride and colleagues summarized 38 case reports of CMLNS and celiac disease worldwide.⁴ CMLNS is typically presented as multiple cystic masses containing milky creamy fluid. On CT, these cystic masses have central low attenuation with a thin enhancing rim, often with fat-fluid levels. CMLNS is associated with a very poor prognosis and up to 50% mortality, mainly due to severe malnutrition, intestinal hemorrhage secondary to ulceration, and overwhelming sepsis, as a combination of hyposplenism plus malnutrition.

Association between CMLNS and EATL is seen much less frequently and, to our knowledge, is described in only two literature cases. In the first case, the CMLNS and EATL developed in a CD patient with persisting symptoms, despite adherence to the gluten-free diet.⁵ The second patient

developed CMLNS and EATL at the terminal ileum and subsequently was diagnosed with CD.⁴ In our patient, EATL with CMLNS was the first presentation of undiagnosed CD. It is not feasible to assess the proper status of CD at that stage, but clinical improvement with a gluten-free diet may indicate that this patient did not have a true refractory disease. We may suggest that, in this case, an absence of a proper diagnosis of CD and continuous load with gluten mimicked refractoriness of the disease.

A validated standard treatment of EATL in patients with CD is lacking. The surgical role is in local debulking and in resection of tumour masses with a high risk of obstruction or perforation. Therapy for CD-associated lymphoma is not different from that used in similar lymphomas in patients without CD. Chemotherapy with anthracycline-containing regimen, like CHOP is the most widely used and is generally responsible for an overall 5-year survival rate of 9–22%. However, in routine practice, chemotherapy cannot be administered in more than one-half of cases due to low performance status, malnourishment from preexisting unresponsive CD, lymphoma dissemination, recurrent infections, and frequently advanced age. In addition, a further 50% of those patients who begin chemotherapy are not able to complete it due to complications, disease relapse, or iatrogenic toxicity.⁶

The Scotland and Newcastle Lymphoma Group published treatment results with chemotherapy regimen IVE/MTX (ifosfamide, vincristine, etoposide /methotrexate), followed by ASCT on newly diagnosed patients with EATL eligible for intensive treatment, followed by auto-stem cell transplantation. Five-year, progression-free survival and overall survival were 52% and 60%, respectively; both are significantly better, compared with the historical group treated with anthracycline-based chemotherapy.⁷ A current trial evaluates pirarubicin in combination with CTOP/ITE/MTX (cyclophosphamide, vincristin, prednisone, ifosfamide, etoposide, and methotrexate) for the de novo young patients with T-cell lymphoma, including EATL.⁸ Administration of radiotherapy is seldom adopted in the treatment of patients with EATL. Novel therapies, including combination of proteasome inhibitor Bortezomib with histone deacetylase inhibitor Panobinostat or Vorinostat, MLN8237 (a Novel Aurora A Kinase Inhibitor) are being evaluated in clinical trials for patients with T-cell lymphomas, including EATL.

Consolidation of chemotherapy with autologous stem cell transplantation is a potential option for patients who can tolerate more intensive treatment. The administration of radiotherapy is seldom adopted in the treatment of patients with EATL.

Conclusion

In conclusion, EATL accompanied by CMLNS is an unusual combination of CD complication with a very poor prognosis. It may be diagnosed in patients without a known history of CD and is a potentially reversible condition that requires early diagnosis. Thus, a high level of clinical suspicion for an overt lymphoma should lead to an extensive work up, including abdominal imaging, endoscopy, and histological examination of gut biopsies. For patients with known history of CD, the strict adherence to a gluten-free diet remains the best option to prevent EATL.

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