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CASE REPORT

Enteropathy-associated T-cell lymphoma presenting with eosinophilia

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ABSTRACT

Hypereosinophilia can be related to various diseases; when it occurs without an obvious cause it is called idiopathic hypereosinophilic syndrome (IHES). We describe a patient with increasing eosinophilia, which in spite of extensive diagnostic procedures initially remained unexplained. However, during follow-up it became apparent that this patient had a lethal enteropathy-associated T lymphoma (EATL) causing the hypereosinophilia.

INTRODUCTION

Hypereosinophilic syndromes (HES) may result either from a myeloid neoplasm or from reactive eosinophilia.[1] Reactive eosinophilia is the result of the action of cytokines and chemokines produced by benign or neoplastic T-helper cells or other cells. Infections, allergies, skin disease, connective tissue diseases and malignancies can all lead to cytokine production by T cells. If no cause can be found, the HES is provisionally designated as idiopathic HES (IHES).[2,3]
Primary intestinal T-cell lymphoma is a rare disease and is often related to coeliac disease. Hence, the new WHO classification designates primary intestinal T-cell lymphomas as enteropathy-associated T lymphoma (EATL).[4] A relationship with eosinophilia, however, is seldom reported, in contrast to other types of T-cell non-Hodgkins lymphoma (T-NHL).[5-8]

We describe a patient with persisting and increasing eosinophilia, which in spite of extensive diagnostic procedures initially remained unexplained. However, during follow-up it became apparent that this patient had an EATL.

CASE REPORT

A 68-year-old male without a relevant medical history presented with a two-week history of a mild cough, slight dyspnoea and pain in his left side. Physical examination at presentation did not reveal any specific signs.
Laboratory analyses showed a white blood cell count of 48.8 x 10^9/l with 85% mature eosinophils. The blood film showed no myeloblasts and a normal morphology of eosinophils. Low values of the plasma total protein (54 g/l) and albumin (26 g/l) (reference range 55-65 g/l and 36-46 g/l, respectively) were noted. Other laboratory values were normal, including the IgE level.
Total protein excretion in the faeces varied between 1.2 and 1.5 g/24 hours, consistent with protein-losing enteropathy. An extensive work-up for allergic, connective tissue, malignant and infectious diseases was negative.
The bone marrow aspirate was hypercellular with 65% mature eosinophils, without evidence of acute leukaemia or chronic myeloproliferative disease. Cytogenetic analysis of the bone marrow showed clonal loss of the Y chromosome. Flow-cytometric analysis of peripheral blood revealed no abnormalities. On duodenoscopy, flattened mucosal folds were seen. The histology showed subtotal villous atrophy, with denudation focally increased intraepithelial lymphocytes (IEL) and cytoplasmic vacuolation indicative of malabsorption. The lamina propria contained an

increased chronic infiltrate with abundant eosinophils. The biopsy was signed out as 'villous atrophy not typical for coeliac disease'. The CT abdomen showed no abnormalities. A provisional diagnosis of IHES was made with probable involvement of the small intestine responsible for a protein-losing enteropathy. Four months later the absolute eosinophil count rose from 48.8 x 10^9/l to 159.0 x 10^9/l in four weeks, with lowering of the serum albumin (24 to 17 g/l). Therapy was started with 60 mg of prednisolone a day, initially leading to a decrease in the eosinophil count to 138 x 109/l, followed by an increase two weeks later. Treatment with hydroxyurea (3 g a day) was initiated because of therapy-resistant IHES. Three days after starting hydroxyurea, the patient was admitted to hospital because of an acute abdomen and an exploratory laparatomy was performed. A mass was found in the distal part of the jejunum and proximal ileum with perforation. Postoperatively the patient became septic and died three weeks after the initial operation because of total respiratory insufficiency due to acquired respiratory distress syndrome (ARDS). At that time the eosinophil count again rose to 265 x 10^9/l, despite continuing hydroxyurea therapy. Consent was not given for a post-mortem examination. Histopathological examination of the resected specimen revealed a bulky transmural tumour with ulceration of the mucosa and localisation in mesenteric lymph nodes. The tumour predominantly consisted of eosinophils intermingled with sheets of monomorphic medium-sized blasts. The adjacent mucosa showed subtle architectural changes without villous atrophy but with a focal increase of IEL.

Detailed immunophenotypic analysis of the, morphologically normal, intraepithelial and subepithelial lymphocytes revealed a substantial population of T cells with an abnormal phenotype: CD2+, CD3+, CD4+, CD7+ and CD5-, CD8- and CD30-. The reversed CD4/CD8 ratio, as compared with IEL of the normal intestine and in uncomplicated coeliac disease, and loss of CD5 were indicative of a neoplastic T-cell proliferation. The phenotype of the tumour mass was CD7+, CD43+, CD45R0+, TIA1+ and focally CD30+, CD2-, CD3-, CD4-, CD5-, CD8-, CD56-, ALK-, CD68-, MPO-, CD79a- and Granzyme-B-.
Additional DNA clonality studies using a PCR heteroduplex analysis of the *TCRG* genes revealed clonal VγI-Jγ1.1/2.1 and VγI-Jγ1.3/2.3 PCR products in the studied colon tissue biopsy,[9] thereby supporting the diagnosis T-NHL.[9,10] Based on the combined histopathological, immunophenotypic and molecular genetic findings we hypothesise that this patient had an EATL associated with a progressive HES.

DISCUSSION

This patient presented with eosinophilia initially interpreted as IHES with involvement of the small intestine, which has been described earlier.[11,12] Conventional cytogenetic analysis of bone marrow cells revealed the clonal loss of the Y chromosome. The frequency of cells with Y loss increases with age and is significantly greater in cases with myelodysplastic syndrome (MDS), myeloproliferative disorder (MPD), B-cell disease and especially acute myelogenous leukaemia than in controls.[13]
However, the follow-up showed the eosinophilia to be a paraneoplastic sign and the leading symptom of a T-NHL classified as an EATL. Although in principal all T-NHL can give rise to eosinophilia this is mostly associated with unspecified peripheral T-NHL.[4] Only a few cases associated with EATL are reported.[5-8] Our case illustrates that in the differential diagnosis of a HES it is insufficient to evaluate T-NHL as a general entity: all clinicopathological entities as described in the WHO classification should be evaluated rigorously.[4]
EATL is difficult to diagnose in an early stage as this disease usually presents with massive abdominal tumour load and perforation. However, in our case, in retrospect the duodenoscopy and biopsy findings were typical for ulcerative jejunitis and provided a clue to the nature of the underlying disease.[7] Because of the known aggressive course and therapy resistance, this most probably would not have changed the clinical outcome. As our case demonstrates, in clinical practice general imaging studies may not be sufficient to rule out the possibility of T-NHL in patients with massive eosinophilia.

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