greater number of diagnostic outcomes would produce wider confidence limits for the kappa statistics if the population size remained the same. It therefore seems that the kappa statistic is not a sensitive indicator of performance in cytopathological or histopathological quality assurance schemes unless large numbers of samples are used. Other indicators should be considered, possibly using systems which weight the outcomes according to the importance of the result in clinical practice. The present study did not include the function of time and the persistence of low kappa statistics over a number of cycles of a quality assurance scheme would be a more reliable indicator of possible unsatisfactory performance. However, the frequency of cycles in most schemes is such that at least two years would elapse before such an assessment would be possible.

1 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74
2 Silcocks PB. Some issues in observer error studies in patholo-

In the initial state of the model $b = 0$ and $c = 0$, and the rest of the cases are split between $a$ and $d$ in the proportions for that particular model (either 50:50 or 80:20 as described in the text). For each iteration of the model $b = b + 1$ and $a = a - 1$—that is, there is replacement of one true negative with a false positive result. For each iteration of the model the parameters given below are calculated.

Observed probability $P_b = \frac{a + d}{i}$

Expected probability $P_e = \frac{\frac{g + h}{i} - \frac{i}{i}}{i}$

$\kappa = \frac{P_b - P_e}{1 - P_e}$

Standard error of $\kappa$ $se = \sqrt{\frac{P_b(1 - P_b)}{i(1 - P_e)^2}}$

95% CI $CI = \kappa \pm (1.96 * s.e.\kappa)$

PPV of a malignant diagnosis $PPV = \frac{d}{d + b}$

Appendix

Diagnosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Benign</th>
<th>Malignant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>$a$</td>
<td>$b$</td>
<td>$g$</td>
</tr>
<tr>
<td>Malignant</td>
<td>$c$</td>
<td>$d$</td>
<td>$h$</td>
</tr>
<tr>
<td>Total</td>
<td>$e$</td>
<td>$f$</td>
<td>$i$</td>
</tr>
</tbody>
</table>

Malignant lymphoma in congenital dyserythropoietic anaemia type III

W G McCluggage, D Hull, E Mayne, H Bharucha, S N Wickramasinghe

Abstract

A 60 year old woman with congenital dyserythropoietic anaemia (CDA) type III developed a malignant T cell lymphoma with cutaneous and widespread nodal involvement. Bone marrow aspirates showed erythroid hyperplasia and dyserythropoiesis with multinucleate erythroblasts and gigantoblasts, in keeping with CDA type III. Electron microscopy showed multinucleate erythroblasts with notably irregular nuclear outlines and intranuclear clefts. The development of malignant lymphoma in this patient, together with a documented high prevalence of monoclonal gammapathy and multiple myeloma and a single case of Hodgkin's disease, may indicate an increased incidence of lymphoproliferative disease in CDA type III.

Keywords: congenital dyserythropoietic anaemia type III, malignant lymphoma, electron microscopy.
The congenital dyserythropoietic anaemias (CDA) are a group of rare, hereditary disorders characterised by the association of refractory anaemia with multinuclearity and other abnormalities of erythroid precursors in the bone marrow. The clinical course is generally benign, although secondary haemochromatosis may develop. The first case of CDA was reported by Wolff and Van Hofe in 1951, who described a family with "familial erythroid multinuclearity". CDA was subsequently classified into three major types by Heimpel and Wendi in 1968: type I, macrocytosis with bone marrow megaloblastoid changes and internuclear chromatin bridges; type II, normocytosis with binucleate and multinucleate marrow erythroblasts and positive acidified serum lysis (Ham's) test; type III, macrocytosis with erythroblast multinuclearity and the formation of gigantoblasts. Cases not fulfilling criteria for type I, II or III have been described subsequently. Recently, a high prevalence of monoclonal gammopathy of undetermined significance and multiple myeloma has been observed in a family with CDA type III. In addition, there has been a single report of Hodgkin's disease in this condition. Here, we describe a patient with long standing CDA type III who developed a malignant T cell lymphoma. Bone marrow aspirate findings and ultrastructural features of erythroid precursors are presented. There may be an increased incidence of lymphoproliferative disease in CDA type III.

Case report

A 43 year old woman was found to be anaemic in 1976 following a routine blood test. At this time the results of a blood count were as follows: haemoglobin, 7.6 g/dl; red blood cell count, 2.2 x 10¹²/l; packed cell volume, 0.23; mean corpuscular volume, 106 fl; mean corpuscular haemoglobin, 35 pg; mean corpuscular haemoglobin concentration, 33 g/dl; reticulocytes, 1 x 10⁹/l; white blood cell count, 4.3 x 10⁹/l; platelets, 175 x 10⁹/l. The patient did not drink alcohol and was not taking medication. There was no family history of anaemia. No lymphadenopathy or splenomegaly was found on clinical examination. Serum vitamin B12 and serum folate were within the normal range. Ham's acidified serum haemolysis test was negative. A bone marrow aspirate was obtained from the iliac crest, the features of which are described later. On the basis of haematological, biochemical and bone marrow aspirate findings, a diagnosis of CDA type III was reached. Several siblings were investigated and had normal blood counts and blood films.

The patient remained well until December 1993 when she developed several raised indurated lesions on the scalp, the histology of which are described later. At that time there was no peripheral lymphadenopathy. A computed tomography (CT) scan of the thorax and abdomen was normal, and a bone marrow aspirate and trephine biopsy specimen revealed no evidence of lymphomatous infiltration. The patient was treated with local radiotherapy.

One year later, in December 1994, the patient developed generalised lymphadenopathy with numerous palpable nodes and CT evidence of mediastinal and pulmonary involvement. A bone marrow aspirate and trephine biopsy specimen again revealed no evidence of lymphomatous infiltration. Lymph node biopsy was performed, the histology of which is described later. Following this, the patient was treated with combination chemotherapy with an initial good response. However, several months later she developed widespread lymphadenopathy which did not respond to treatment. She died in December 1995.

Methods

Bone marrow smears were stained with May-Grunwald-Giemsa. Trephine biopsy specimens were processed in plastic using the epoxy resin method. Paraffin wax sections were stained with haematoxylin and eosin. The excised skin nodules and lymph node were fixed in formalin, routinely processed in paraffin wax and stained with haematoxylin and eosin. Immunohistochemical staining of tissue sections was performed using a standard Streptavidin biotin peroxidase method (Dako, High Wycombe, UK). Sections were stained with the following antibodies: LCA (leucocyte common antigen, CD45 monoclonal), UCHL1 (CD45RO, monoclonal), CD3 (monoclonal), CD2 (CD20 monoclonal), CD15 (monoclonal), and CD30 (Ber-H2, monoclonal) (all from Dako). Immunohistochemical staining was carried out using appropriate positive and negative controls. Electron microscopy was performed on plastic embedded bone marrow trephine biopsy tissue. Ultrathin sections were stained with uranyl acetate and lead citrate.

Results

BONE MARROW ASPIRATES

Bone marrow aspirates taken in 1976, 1993 and 1994 showed identical features. The cellularity of marrow fragments was normal. There was evidence of erythroid hyperplasia, the megakaryocyte:erythroid ratio being reduced to 0.78. A significant proportion of basophilic and polychromatophilic erythroblasts showed dyserythropoietic features. Four percent of erythroblasts were binucleate (normal < 0.57%) and 1.1% had three to eight nuclei (fig 1A). Individual nuclei within binucleate or multinucleate erythroblasts were sometimes unequal in size and were occasionally different in shape and staining characteristics. Other dyserythropoietic features included Howell–Jolly bodies in 0.65% of erythroblasts (normal < 0.4%). Notably irregular nuclear outlines in 1.42% of mononuclear erythroblasts (normal < 0.5%) and coarse basophilic stippling of the cytoplasm. Rare giant mononuclear erythroblasts were present. Internuclear chromatin bridges (a characteristic finding in CDA type I) were not present. Some macrophages contained phagocytosed erythroblasts.
ELECTRON MICROSCOPY
Ultrastructural examination of bone marrow showed many binucleate and multinucleate erythroblasts (fig 1B). Sometimes, individual nuclei in the same erythroblast differed in size and shape. Nuclear outlines were irregular, some nuclei containing deep clefts. In some areas there was loss of nuclear membrane material. Several nuclei were undergoing karyorrhexis. No myelin figures or other distinctive cytoplasmic features were observed.

PATHOLOGY
Histology of the scalp lesions showed unremarkable surface stratified squamous epithelium. Beneath a narrow Grenz zone, a dense infiltrate of lymphoid cells extended from the superficial dermis into subcutaneous adipose tissue (fig 2). The infiltrate largely consisted of mononuclear cells with vesicular nuclei, prominent nucleoli, irregular nuclear outlines, and a moderate amount of cytoplasm. Immunohistochemistry showed diffuse strong positive staining with LCA and T cell markers UCHL1 and CD3 (fig 2). There was little or no staining with the B cell marker L26 or with CD15 and CD30. The histological diagnosis was high grade, non-Hodgkin’s, T cell lymphoma. The excised lymph node was infiltrated by cells identical with those in the skin lesions. Immunohistochemistry confirmed nodal involvement by T cell lymphoma.

Discussion
CDA type III is a rare disorder of erythropoiesis, characterised by macrocytosis and the presence in the bone marrow of giant multinucleate erythroblasts (gigantoblasts) with up to 10 nuclear masses per cell, in the absence of vitamin B12 or folate deficiency. Giant mononuclear erythroblasts may also be present and erythroblasts may exhibit basophilic stippling of the cytoplasm and karyorrhexis. Granulocyte precursors and megakaryocytes generally exhibit a normal morphology although electron microscopy may reveal abnormalities in megakaryocytes. The disease is usually indolent with mild to moderate anaemia, sometimes with episodes of jaundice and fatigue due to haemolysis. At least two different patterns of inheritance have been documented, some families exhibiting an autosomal dominant pattern and others autosomal recessive. Ultrastructural abnormalities have been described in mononuclear and multinucleate erythroblasts in CDA type III. These have included intranuclear clefts, grossly disorgan...
Duodeno–jejunal adenocarcinoma as a first presentation of coeliac disease

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Abstract

Long standing coeliac disease is associated with an increased risk of malignancy, not only of intestinal lymphoma but also small intestinal adenocarcinoma. Two patients whose initial presentation was adenocarcinoma of the small bowel, but who were subsequently found to have coeliac disease after Whipple’s resection, are described. The diagnosis was made early in the postoperative period in the first patient after close histological examination of the tumour-free mucosal margins. This patient was placed on a gluten-free diet and had an uncomplicated postoperative recovery with rapid weight gain. Diagnosis and dietary intervention in the second patient was very delayed and resulted in the development of severe malabsorption and weight loss. This illustrates the importance of ruling out coeliac disease prior to surgery in patients with small intestinal malignancies. (J Clin Pathol 1996;49:602–604)

Keywords: small bowel, adenocarcinoma, coeliac disease.