Short reports

Angiotropic lymphoma: report of a case with histiocytic features

J A Snowden, C A Angel, D A Winfield, J H Pringle, K P West

Abstract

Angiotropic lymphoma, also known as intravascular lymphomatosis, is characterised by widespread intravascular proliferation of malignant lymphoid cells, usually without evidence of focal disease. A case of a 52 year old man referred for investigation of a two year history of pyrexia of unknown origin, skin rash and multiple organ failure is described. Angiotropic lymphoma was seen in gastric, colonic and skin biopsy specimens, and review of an earlier skin biopsy specimen showed similar morphological features. In contrast to previous cases which showed B or T cell differentiation, immunohistochemical examination was positive for histiocyte markers. Molecular studies showed no evidence of immunoglobulin heavy chain gene or T cell receptor gene rearrangement. The patient responded to combination chemotherapy, comprising cyclophosphamide, doxorubicin, etoposide, and prednisolone. This case highlights the fact that advanced lymphoma may be present without evidence of focal disease and that the diagnosis may be missed easily both clinically and histologically.

(*J Clin Pathol* 1997;50:67-70)

Keywords: angiotropic lymphoma; histiocytes.

Angiotropic lymphoma was subsequently diagnosed and the patient made a good response to chemotherapy.

Case report

A 52 year old man of previous good health first presented to another hospital in April 1991 with fever and sweats, general malaise, weight loss, and an erythematous rash on the inner thighs. Except for pyrexia (39.2°C), the rash and pallor, clinical examination was normal. Haematologically, there was a normochromic, normocytic anaemia (haemoglobin concentration 8.4 g/dl) and thrombocytopenia ($66 \times 10^9/l$), with red cell fragmentation but normal coagulation profile and reactive appearances on a bone marrow aspirate and a trephine biopsy specimen. Biochemically, there was a small increase in his serum urea concentration (9.8 mmol/l) but normal electrolyte and creatinine concentrations, and normal urinalysis. Serum albumin had fallen to 23 g/l, and there was mild derangement of other liver function tests. Bacteriological, serological and immunological screens were negative. Chest x ray, abdominal and cardiac ultrasound scans, small bowel meal, and a computed tomography scan were normal. Skin and liver biopsy specimens were reported as showing numerous leucocytes in dilated dermal vessels and dilated sinusoids, respectively, but no conclusive diagnosis was reached. The patient was treated with broad spectrum antibiotics and antituberculous therapy to which there was no response. A trial of prednisolone and naproxen was prescribed resulting in a resolution of the pyrexia and gradual correction of the anaemia, hypoalbuminaemia, and renal and liver function. The patient was discharged with a working diagnosis of autoimmune disease and over the following three months the steroids and naproxen were tailed off without symptomatic relapse.

Eight months after presentation, the patient's symptoms and laboratory abnormalities recurred and again partially responded to prednisolone and naproxen, but by August 1992 his clinical condition had deteriorated and on this occasion failed to respond to other treatment including azathioprine. At the time of referral and re-investigation in February

Department of
Haematology, Royal
Hallamshire Hospital,
The Central Sheffield
University Hospitals
Trust, Glossop Road,
Sheffield S10 2JF

J A Snowden
D A Winfield

Department of
Pathology,
University of Sheffield
Medical School,
Beech Hill Road,
Sheffield S10 2RX
C A Angel

Department of
Pathology, University
of Leicester Medical
School, Leicester
Royal Infirmary,
PO Box 65,
Leicester LE2 7LX
J H Pringle
K P West

Correspondence to:
Dr C A Angel.

Accepted for publication
30 September 1996

Figure 1 Gastric biopsy specimen showing dilated capillaries containing large cells with abundant cytoplasm.

Figure 2 Skin biopsy specimen showing dilated dermal capillary containing tumour cells and thrombus.

1993, 22 months after his initial presentation, he was an ill, wasted, semi-conscious man with persistent culture negative diarrhoea. On examination, he had a pigmented urticarial rash affecting mainly the neck and shoulders and a peripheral sensory neuropathy to pinprick and vibration in the hands and feet.

Upper and lower gastrointestinal endoscopy revealed gross mucosal oedema and multiple telangiectatic vessels. Gastric biopsy specimens showed expansion of the lamina propria by numerous dilated and proliferating capillaries lined by flat endothelial cells and containing large cells with abundant eosinophilic cytoplasm and prominent erythrophagocytosis, mildly irregular nuclei and occasional nucleoli (fig 1). Similar features were present in duodenal and colonic biopsy specimens. A skin biopsy specimen showed numerous dilated dermal capillaries containing similar cells admixed with thrombus (fig 2), and was very similar to the biopsy specimen taken at presentation. In retrospect, a liver biopsy specimen taken shortly after presentation also contained very occasional small capillaries containing similar cells. Bone marrow aspiration and a trephine biopsy specimen showed no evidence of disease.

Paraffin wax sections of the gastric and skin biopsy specimens were examined immunohistochemically using a panel of antibodies (table 1) and a routine avidin-biotin complex technique. The intravascular cells showed strong cytoplasmic positivity with Mac 387 (fig 3), and definite but weaker expression of CD68, S100, CD45, CD43, lysozyme, and α -1-antichymotrypsin. All other markers of B or T lymphoid lineage (CD45RA, CD45RO, CD20, and CD3) were negative. CD34

(QBend10) stained vascular endothelium clearly, but the intravascular cells were negative. All other markers were negative.

DNA was extracted from frozen biopsy material for antigen receptor gene analysis. EcoR1, BamH1 and HindIII digested DNA was probed with an immunoglobulin heavy chain joining region probe, J_H, and a T cell receptor β chain constant region probe, as described previously,⁴ but no evidence of clonal rearrangement was seen. PCR using primers for the immunoglobulin heavy chain gene and β chain gene of the T cell receptor⁵ also failed to show evidence of clonal rearrangement.

The patient was treated with combination chemotherapy (cyclophosphamide 650 mg/m², doxorubicin 25 mg/m², etoposide 100 mg/m² on days 1 and 8 with prednisolone 50 mg/m² on days 1–8), receiving a total of six cycles of treatment. The patient's clinical and laboratory abnormalities returned to normal and he remained in remission after treatment for 27 months. In June 1995, he again developed anaemia and skin rash, and a duodenal biopsy specimen showed histological evidence of recurrence. Chemotherapy induced a second remission and he remains well 14 months later.

Discussion

Pfleifer and Tappeiner, in 1959, were the first to describe extensive intravascular proliferation of atypical mononuclear cells as 'angioendotheliomatosis systemisata'.⁶ Subsequently, more than 15 synonyms have been used to describe the disorder.¹ Earlier reports assumed an endothelial origin, whereas others suggested that the atypical cells were disseminated carcinoma cells with an unknown primary.¹ Once immunohistochemical methods and gene rear-

Table 1 Antibodies used

CD	Antibody	Specificity
45	LCA	B cells and most T cells, macrophages, myeloid cells
20	L26	B cells, sometimes macrophages
45RA	MB1	B cells, subpopulation of T cells
	MB2	B cells, some macrophages
79a	Anti-CD79a	B cells
3	Anti-CD3	T cells
43	MT1	T cells, some macrophages, granulocytes, erythroid cells, Langerhans cells
45RO	UCHL1	T cells, some macrophages, granulocytes
	Mac 387	Macrophages, some myeloid cells
68	PGM1	Macrophages
	KP1	Macrophages
	S100	Langerhans cells, interdigitating reticulum cells, some follicular dendritic cells
15	Leu M1	Granulocytes, some macrophages
30	Ber H2	Activated B and T cells, some macrophages
34	QBend10	Some haematological and lymphoid precursor cells, endothelial cells
	Lysozyme	Myeloid cells, monocytes, macrophages
	α -1-antichymotrypsin	Monocytes, macrophages

Adapted from Warnke *et al.*³

Figure 3 Gastric biopsy specimen showing strongly positive reaction of the tumour cells with Mac 387.

range analysis became available, however, it became apparent that virtually all cases were monoclonal proliferations of B,^{1,2} and occasionally T, lymphoid cells,² whereon the terms angiotropic lymphoma and primary intravascular lymphomatosis were adopted.

The case reported here shows many similarities to angiotropic lymphoma, but is unusual in that the putative neoplastic cells had histological and immunophenotypic features of histiocytes. It is therefore tempting to speculate that this lesion is not lymphoma but a malignant proliferation of histiocytes. It is, however, well known that many lesions thought to be histiocytic malignancies have, with the advent of modern immunophenotypic and molecular biological techniques, been shown to be T cell, or less frequently B cell, malignancies.⁷ The criteria for defining histiocytic malignancy are

difficult but have been described recently by Cline.⁸ Although this case shows some of the enzymatic, immunophenotypic and functional characteristics of histiocytes, few, if any, of these are unique to histiocytes, and there is no definitive evidence that the reported case is clonal. Under these circumstances, we propose that the lesion should be regarded as a subtype of angiotropic lymphoma, the cells of which resemble histiocytes.

O'Grady *et al*⁹ have recently described an apparently similar case which they also postulate is a variant of angiotropic lymphoma. This case was localised to the skin and showed no evidence of systemic involvement. The cells showed very similar histological features and expressed similar markers in paraffin wax embedded material, although S100 was not present. Whether these apparent variants of angiotropic lymphoma have a very different clinical course to typical examples is uncertain. Most previously reported cases have fever and multiorgan dysfunction, with skin and central nervous system involvement. In our case, the central nervous system was apparently spared, but there was peripheral nerve involvement, presumably as a result of involvement of epineural and perineural vessels.¹⁰ Like many previous cases, the presentation not only mimicked but was mistaken for autoimmune disease.¹¹ An association with disseminated intravascular coagulation has been noted previously and microangiopathic anaemia was a feature in our patient, possibly related to fragmentation of the erythrocytes in the microvasculature.¹²

The optimal management and prognosis of angiotropic lymphoma is not clear.¹³ The diagnosis is often missed until the later stages, and in many reports the diagnosis is made at necropsy. The recognition of lymphoid origin led to the use of anti-lymphoma chemotherapy. Success rates are variable, some patients responding poorly¹ but others,¹³ including our patient, sustaining remission. Immunophenotype correlates with prognosis in other types of lymphoma but it remains to be seen whether angiotropic lymphoma with histiocytic features generally has a good prognosis. The fact that the chemotherapeutic regimen contained etoposide, which is effective in both Langerhans cell and malignant histiocytosis, may have been pivotal in this case.¹⁴

In conclusion, this case illustrates several points. Firstly, angiotropic lymphoma may express markers of histiocytic differentiation. Secondly, lymphoma may be present without any evidence of focal disease and may be mistaken for connective tissue disease. Biopsy of affected organs coupled with recognition of the often subtle histological features is important in such cases. If the diagnosis is missed, the patient will progress inexorably to death. If, however, the diagnosis is made, there is opportunity for lasting remission and potential cure.

1 Molina A, Lombard C, Donlon T, Bangs CD, Dorfman RF. Immunohistochemical and cytogenetic studies indicate that malignant angioendotheliomatosis is a primary intravascular (angiotropic) lymphoma. *Cancer* 1990;66:474-9.

- 2 Clark WC, Dohan FC Jr, Moss T, Schweitzer JB. Immunocytochemical evidence of lymphocytic derivation of neoplastic cells in malignant angioendotheliomatosis. *J Neurosurg* 1991;74:757-62.
- 3 Warnke RA, Weiss LM, Chan JKC, Cleary ML, Dorfman RF. Fascicle 14. Tumors of the lymph nodes and spleen. In: *Atlas of tumor pathology*. 3rd series. Washington DC: Armed Forces Institute of Pathology, 1995.
- 4 Angel CA, Pringle JH, Naylor J, West KP, Lauder I. Analysis of antigen receptor genes in Hodgkin's disease. *J Clin Pathol* 1993;46:337-40.
- 5 Angel CA, Pringle JH, Primrose L, Lauder I. Detection of immunoglobulin heavy chain gene rearrangements in Hodgkin's disease using PCR. *J Clin Pathol* 1993;46:940-2.
- 6 Pfeiffer I, Tappeiner J. Zur Kenntnis des systemisierten. Endotheliomatose der curanen Blutgefasse. *Hautarzt* 1959;10:359-633.
- 7 Weiss LM, Trela MJ, Cleary ML, Turner RR, Warnke RA, Sklar J. Frequent immunoglobulin and T-cell receptor gene rearrangements in "histiocytic" neoplasms. *Am J Pathol* 1985;121:369-73.
- 8 Cline MJ. Histiocytes and histiocytosis. *Blood* 1994;84:2840-53.
- 9 O'Grady JT, Shahidullah H, Doherty VR, Al-Nafussi A. Intravascular histiocytosis. *Histopathology* 1994;24:265-8.
- 10 Prayson RA. Angiotropic large cell lymphoma: simultaneous peripheral nerve and skeletal muscle involvement. *Pathology* 1996;28:25-7.
- 11 Kao NL, Broy S, Tillawi I. Malignant angioendotheliomatosis mimicking systemic necrotizing vasculitis. *J Rheumatol* 1992;19:1133-5.
- 12 Stahl RL, Chan W, Duncan A, Corley CC Jr. Malignant angioendotheliomatosis presenting as disseminated intravascular coagulation. *Cancer* 1991;68:2319-23.
- 13 Williams DB, Lyons MK, Yanagihara T, Colgan JP, Banks PM. Cerebral angiotropic large cell lymphoma (neoplastic angioendotheliomatosis): therapeutic considerations. *J Neurol Sci* 1991;103:16-21.
- 14 Ceci A, de Terlizzi M, Colella R, Balducci D, Toma MG, Zurlo MG. Etoposide in recurrent childhood Langerhans' cell histiocytosis: an Italian cooperative study. *Cancer* 1988;62:2528-31.

J Clin Pathol 1997;50:70-71

Involvement of the appendix in pseudomembranous colitis

J D Coyne, P A Dervan, N Y Haboubi

Abstract

Pseudomembranous colitis (PMC) is an inflammatory disorder usually limited to the large intestine and is the consequence of antibiotic associated *Clostridium difficile* overgrowth with production of its toxin. It has a characteristic gross and microscopic appearance. PMC-like changes, usually associated with perioperative hypotension and with more extensive gastrointestinal tract involvement, have also been described. In neither clinical setting has pseudomembranous appendicitis been recorded. A case of pseudomembranous appendicitis in a 76 year old woman is described.

(*J Clin Pathol* 1997;50:70-71)

Keywords: appendix; pseudomembranous colitis; pseudomembranous appendicitis.

Pseudomembranous colitis (PMC) is an inflammatory disorder usually limited to the large intestine and is the consequence of antibiotic associated *Clostridium difficile* overgrowth with production of its toxin.¹ It has a characteristic gross and microscopic appearance. PMC-like changes, usually associated with perioperative hypotension and with more extensive gastrointestinal tract involvement, have also been described.² In neither clinical setting has pseudomembranous appendicitis been recorded and we therefore wish to document its occurrence.

Case report

A 76 year old woman on haemodialysis for chronic renal failure developed rigors. Blood

cultures grew staphylococcus and she was treated with clindamycin. The patient developed abdominal pain and diarrhoea, and a diagnosis of pseudomembranous colitis was confirmed on colonoscopy and biopsy appearances. She was treated conservatively, given metronidazole and settled. Four weeks later, the patient was readmitted with recurrent pseudomembranous colitis. Because she was unresponsive to further conservative treatment, a proctocolectomy was performed. The patient died of septic shock five days later.

Pathology

The proctocolectomy specimen measured 70 cm in length with an attached appendix 6 cm in length. Multiple diverticula were present over almost the entire length of the transverse and descending colon. The mucosal surface showed diffuse disease with areas of ulceration alternating with adherent greenish membranes. Microscopic examination showed the typical appearances of pseudomembranous colitis with well-formed intracryptal summit lesions (type I) and type II lesions composed of dilated and disrupted crypts, showing partial destruction and surmounted by an explosive exudate of neutrophils and fibrin. There was extensive involvement of the diverticula and sections of the appendix showed typical lesions involving the mucosal surface (figs 1 and 2).

Examination of our records revealed five other colectomy specimens submitted to our laboratories with pseudomembranous colitis during the preceding 20 years. The patients' ages ranged from 47 to 77 years and three of these had a history of antibiotic usage with

Department of
Histopathology, South
Manchester University
Hospitals NHS Trust,
Manchester
J D Coyne
N Y Haboubi

Department of
Pathology, The Mater
Hospital, University
College Dublin,
Dublin, Ireland
P A Dervan

Correspondence to:
Dr J D Coyne, Department
of Histopathology, South
Manchester University
Hospitals NHS Trust,
Withington Hospital, Nell
Lane, Manchester M20 8LR.

Accepted for publication
30 September 1996