Immunoblastic lymphadenopathy: evolution into immunoblastic sarcoma

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SUMMARY A case of immunoblastic lymphadenopathy which underwent transformation into immunoblastic sarcoma is reported. A 64-year-old man presented with a rash, generalised lymphadenopathy, and hepatosplenomegaly. A cervical lymph node removed at biopsy showed the features of immunoblastic lymphadenopathy with the presence of heavy chain classes IgG, IgM, and IgA and both kappa and lambda light chain types in the cytoplasm of the immunoblasts. No such immunoglobulins could be demonstrated in the lymph nodes obtained at necropsy when the patient died of widespread immunoblastic sarcoma. The biological evolution and histogenesis of the disease are discussed and the current literature is reviewed.

Immunoblastic lymphadenopathy (IBL) or angioimmunoblastic lymphadenopathy with dysproteininaemia (AILD) is a recently recognised clinicopathological entity. It has been considered to be a non-neoplastic hyperimmune state caused by an abnormal proliferation of B lymphocytes with an associated defect of T-cell regulatory functions. Clinically, the disease occurs predominantly in the elderly and is characterised by acute constitutional symptoms, cutaneous rash, generalised lymphadenopathy, and hepatosplenomegaly. Polyclonal hyperglobulinaemia and haemolytic anaemia are frequently present. Histologically, the lymph nodes show proliferation of immunoblasts, plasmacytoid immunoblasts, plasma cells, and arborising blood vessels and the presence of acidophilic hyaline interstitial material (Frizzera et al., 1974; Lukes and Tindle, 1975). The number of cases undergoing transformation into malignant lymphoma or immunoblastic sarcoma ranges from 0 to 35% (Frizzera et al., 1974; Nathwani et al., 1978). This complication of IBL has been documented infrequently in the British literature. We report a case of IBL that underwent transition to an immunoblastic sarcoma (IBS) and give the immunohistochemical and necropsy findings.

Case report

A 64-year-old supervisor in a cotton mill was admitted to the Royal Infirmary at Blackburn in May 1976. He had been ill for about two months, initially having abdominal pain which spontaneously subsided and was followed after two weeks by an itchy rash at first confined to the abdomen and later spreading to the thighs. Concurrently, he was noticed by his general practitioner to have enlarged cervical lymph nodes and hepatosplenomegaly. Ten days before admission he had become febrile with episodic sweating and rigors. There was no history of drug ingestion before the illness and there had been no loss of weight. The past medical history and family history were uneventful except that his 27-year-old son had recently been treated for toxoplasmosis.

On admission he was well nourished and not anaemic. There was a generalised, discrete, mobile, non-tender lymphadenopathy. The spleen was felt 4 cm below the costal margin and the liver was just palpable. Dullness was present at the base of the left lung, suggesting a small effusion, and he had a tachycardia of 100 with an audible fourth heart sound. There was an itching rash on the trunk, upper arms, and thighs; in part this was macular, but there were also large, confluent, violaceous areas. A clinical diagnosis of lymphoreticular disease or systemic lupus erythematosus was made.

Investigations revealed a haemoglobin of 14.3 g/dl; WBC $10 \times 10^9$ with 7% eosinophils; serum alkaline phosphatase 77 IU/l; IgM 2.8 g/l; IgA 0.9 g/l; IgG 11.5 g/l. Toxoplasma dye test showed a titre of 1/128. Chest x-ray confirmed the presence of a small left-
sided effusion but the lung fields were otherwise clear. A lymph node was removed from the neck, and a diagnosis of immunoblastic lymphadenopathy was made. The patient was transferred to the Christie Hospital and Holt Radium Institute under the care of Professor Derek Crowther in June 1976. By this time he had developed some pedal oedema. The rash was fading but he still had pruritus. The diagnosis was confirmed and it was decided initially not to give any therapy. He was discharged home. However, in August 1976 treatment with prednisolone was started and he was given two courses of chlorambucil. He was readmitted to the Christie Hospital in February 1977 with increasing dyspnoea and back pain. He was found to have a mild proximal myopathy and a slightly larger left-sided effusion. There was collapse of the body of T12 vertebra. The prednisolone was stopped. In March 1977 he was readmitted to a hospital in Blackburn in a terminal state with spinal cord compression due to collapse of T12 vertebra and died four days later.

**Pathology**

*Surgical specimen*

The cervical lymph node (1·5 × 1·0 × 1·0 cm) was firm with a greyish-white cut surface. Paraffin sections were stained with haematoxylin and eosin, periodic-acid Schiff (PAS), reticulin, elastic van Gieson, and methyl green pyronin.

The lymph node showed loss of normal architectural pattern with obliteration of the peripheral sinuses and lymphoid follicles. The cellular infiltrate was polymorphic and consisted of large numbers of immunoblasts, plasmacytoid immunoblasts, and plasma cells. The immunoblasts were large cells (Fig. 1), varying in size between 15 and 25 μ in diameter with well-circumscribed cell margins; the cytoplasm of the immunoblasts showed marked pyroninophilia. The nuclei of the immunoblasts were round or oval in shape and contained one or two prominent nucleoli. Plasmacytoid immunoblasts were cells containing eccentric nuclei with amphiphilic

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**Fig. 1** IBL. Cervical lymph node showing immunoblasts which contain large nuclei with prominent nucleoli (single arrow). Note a binucleate immunoblast (double arrows). Haematoxylin and eosin × 600.
lic cytoplasm in the H and E sections (Fig. 2); these cells showed cytoplasmic pyroninophilia in sections stained with methyl green pyronin. Cells intermediate in differentiation between lymphocytes and plasma cells were also present. No Reed-Sternberg cells were seen. Scattered non-neoplastic reactive histiocytes were also present. Eosinophils were not seen.

The reticulin and elastic van Gieson stains showed prominent arborising postcapillary venules with prominent endothelial cells (Fig. 3). PAS-positive hyaline interstitial material was present, especially in the cortical areas (Fig. 4).

**Necropsy**

Necropsy was carried out 3 hours after death. The skin and conjunctivae showed moderate pallor. No skin rash was present. No icterus, cyanosis, or clubbing was present. Lymphadenopathy was generalised, involving the cervical, axillary, and inguinal lymph nodes. The heart (275 g) was normal in configuration except the right atrial appendage, which was dilated and contained an antemortem thrombus. No cause was found for the thrombosis. The free wall of the right ventricle and the left ventricle with the septum weighed 50 g and 175 g respectively. The valves were normal. There was no evidence of infective endocarditis. The coronary arteries and their major branches showed moderate atheroma with partial occlusion of their lumina. The aorta and major arteries showed moderate atheroma. The right and left pulmonary arteries contained fairly recent antemortem thrombi. The major systemic veins were normal. Dissection of the deep veins in the lower limbs did not show any thrombi.

The airways showed the presence of acute inflammatory exudate. The right and left lungs (330 g and 450 g respectively) showed mild centrilobular emphysema involving the upper lobes and oedema, congestion, and bronchopneumonia involving the lower lobes. No pulmonary infarction was seen.

The gums did not show any gingival hyperplasia. The oesophagus showed slightly raised nodules of glycogenic acanthosis. The stomach showed two acute ulcers (0.5 and 1.0 cm) on the lesser curvature. The small and the large intestines were normal. The

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**Fig. 2** 1BL. Cervical lymph node showing an admixture of plasma cells, plasmacytoid immunoblasts (arrow), and lymphocytes. The plasmacytoid immunoblasts contain eccentric nuclei, and their cytoplasm is amphiphilic. Haematoxylin and eosin × 614.
liver (1750 g) showed mild fatty change and an exaggerated lobular pattern. No discrete tumour nodules were seen in the liver. The kidneys (125 g each) showed mild cortical pallor. The urinary bladder had an inflamed mucosa. The prostate (35 g) showed nodular hyperplasia. The testes were normal.

The cranial meninges did not show any tumour deposits. The cerebrum, cerebellum, and brainstem (1300 g) were normal. The spinal dura mater showed compression collapse due to extensive tumour deposition. The other vertebrae were free from tumour.

The thymus was not identified in the anterior mediastinum. The paratracheal and hilar lymph nodes were enlarged (0.5-3.0 cm in diameter) and firm in consistency and showed greyish-white cut surfaces. The cervical, axillary, and inguinal lymph nodes were enlarged (1.0-3.0 cm in diameter) and showed replacement of normal structure by greyish-white tumour tissue. The superior pancreatic, porta hepatic, mesenteric, pre- and para-aortic, and pelvic lymph nodes were markedly enlarged (2.0-4.0 cm in diameter) and showed appearances similar to those of the superficial lymph nodes. The tonsils were not enlarged. The spleen (910 g) was markedly enlarged and showed numerous discrete tumour nodules (0.2-0.4 cm in diameter).

At necropsy the immediate cause of death was considered to be pulmonary embolism from a fragmented thrombus in the right atrial appendage.

The blocks of tissue obtained at necropsy were fixed in buffered formalin and embedded in paraffin. The sections of the lymph nodes obtained at necropsy were subjected to the special stains as given above. These lymph nodes showed replacement of structure by an admixture of large lymphoid cells, immunoblasts, and plasmacytoid lymphocytes (Fig. 5). The degree of cytoplasmic pyroninophilia in the immunoblasts was reduced. Acidophilic hyaline interstitial material was not present. There was proliferation of arborising blood vessels, but this was not as prominent a feature as is seen in IBL. The spleen and the portal tracts of the liver showed cellular infiltrates
Fig. 4  **IBL.** Hyaline interstitial material in cervical lymph node. × 384.

Fig. 5  **IBS.** Lymph node removed at necropsy shows replacement of structure by an admixture of immunoblasts, large lymphoid cells, and plasmacytoid lymphocytes. Haematoxylin and eosin × 800.
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similar to those in the lymph nodes. The bone marrow of the 12th thoracic vertebral body showed replacement of its normal cell components by immunoblasts and large lymphoid cells (Figs 6 and 7). Sections from the lungs were stained for fungi and protozoa. No fungi or pneumocystis carinii were seen in the lungs. Apart from the changes of pneumonia, the lungs did not show any immunoblastic infiltrates nor was there any interstitial pulmonary fibrosis. No evidence of vasculitis was seen in any organs. Stains for amyloid were negative.

IMMUNOHISTOCHEMISTRY

Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded sections from the surgical lymph node biopsy specimen and from lymph nodes obtained at necropsy. The sections were initially treated with 2% trypsin at 37°C for 10 minutes in order to increase the sensitivity of the immunoperoxidase staining method (Curran and Jones, 1978). Immunoperoxidase stains were performed on all the sections at the same time using antisera to heavy chain classes IgG, IgM, and IgA and both kappa and lambda light types and employing appropriate serum controls (Sternberger, 1974). The surgical lymph node biopsy showed positive staining reactions to IgG (Fig. 8), IgM, IgA, kappa and lambda chains whereas the sections from the lymph nodes removed at necropsy failed to demonstrate any such immunoglobulins (Fig. 9).

Discussion

Immunoblastic lymphadenopathy is an uncommon entity. We know very little about the histogenetic and pathogenetic mechanisms of the disease. Lukes and Tindle (1975) expressed the view that IBL occupies a position intermediate between the spectrum of benign compensatory immunoblastic reaction and immunoblastic sarcoma. The basic process, according to these workers, is a 'switch-on' in the transformation of the B-cell system triggered by a hypersensitivity reaction to drugs. A history of drug hypersensitivity reaction was present in 27% of their cases. The incriminating drugs have been penicillin, griseofulvin, diphenylhydantoin (Lapes

Fig. 6 IBS. Bone marrow obtained at necropsy shows replacement of structure by immunoblasts and large lymphoid cells. Haematoxylin and eosin × 375.
et al., 1976), and methyl dopa (Weisenburger, 1978). The drugs probably act as haptens to self-antigens and sensitize the B-lymphocytes after bypassing the T-cell dependent tolerance (Flax, 1974). There was no history of drug hypersensitivity in our case.

The biological evolution of the disease process in IBL is unpredictable. The course of the disease is usually progressive, although sometimes long-term clinical remission may be found. The median survival in 18 fatal cases was 15 months (Lukes and Tindle, 1975).

Nathwani et al. (1978) made the diagnosis of IBL when one or more of the following microscopic features were associated with or preceded by the histological appearance of angioimmunoblastic lymphadenopathy: (1) multiple, dense, and well-delineated clusters of large lymphoid cells; (2) islands of less dense and ill-circumscribed extravascular cells; and (3) diffuse proliferation of large lymphoid cells with marked reduction in the number of lymphocytes. The large lymphoid cells may show a variable degree of plasmacytoid appearances or there may be an admixture of lymphoid cells of intermediate size as well as typical and atypical plasma cells. Our case showed an admixture of large lymphoid cells, immunoblasts, and plasmacytoid lymphocytes in the lymph nodes, spleen, and marrow of the 12th thoracic vertebral body obtained at necropsy. The histological appearances resembled those of poorly differentiated, diffuse, lymphohistiocytic lymphoma.

Evolution of malignant lymphoma or immunoblastic sarcoma in IBL could be explained by an attractive hypothesis of ‘two-hit phenomenon’ which has been postulated in the pathogenesis of B-cell neoplasia (Salmon and Seligmann, 1974). IBL is the expression of the ‘first hit’ and occurs as a result of exposure to an antigen which leads to monoclonal B-cell proliferation. This is the preneoplastic stage. The ‘second hit’ is the oncogenic stimulus or a mutagenic stimulus which transforms a susceptible subclone into a neoplastic growth. Immunoblastic sarcoma is thus an expression or effect of the second hit. On the other hand, development of follicular-centre-cell type of non-Hodgkin lymphoma and IBL could have a common denominator, namely, a block in the transformation of ‘switch-on’ or derepression from cleaved to non-cleaved cells (Lukes and Collins, 1974).

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between IBL and graft versus host reaction (GVHR). GVHR commonly evolves as lymphoid depletion or lymphoreticular neoplasia. On this basis it is not unusual for IBL to undergo transformation into malignant lymphoma or IBS. The defect is probably a deficiency of T-cell regulatory function, which predisposes to an abnormal proliferative and auto-aggressive reaction of the B-cell system (Frizzera et al., 1975).

Attempts have been made to determine the lineage of the immunoblast in IBL. An immunoblast, by definition, is a transformed lymphocyte which becomes a hyperbasophilic pyroninophilic blast cell as a result of exposure to a mitogen in vitro (Dameshek, 1963). On the basis of associated proliferation of plasmacytoid immunoblasts and plasma cells and the presence of hyperglobinaemia, Lukes and Tindle (1975) have suggested a B-cell origin of the immunoblast in IBL. In a study involving surface membrane immunoglobulin, E-rosette formation, and complement receptor bearing cells, Rudders and DeLellis (1977) have shown that there was proliferation of both B- and T-lymphocytes in the lymph node in IBL with numerical predominance of T-cells. Anomalies of T-cell regulatory function in IBL are expressed by a high mortality rate due to opportunistic infections, cutaneous anergy, autoimmune haemolytic anaemia, and prevalence of the disease during senescence. Depletion of T-cells in the peripheral blood has been recorded (Neiman et al., 1978). The possibility of a lympholytic factor (Lukes and Tindle, 1975) or of a lymphocytotoxin in the peripheral blood cannot be entirely excluded.

Fisher et al. (1976) described a case of IBL which underwent transformation into malignant lymphoma. Ultrastructural, cytochemical, and immunological studies in this case revealed that the neoplastic cells had plasmacytoid features. Polyclonal intracellular immunoglobulins of heavy chain classes IgG, IgM, IgA, and kappa and lambda light chain types were also demonstrated in the plasma cells and 'reticular lymphoblasts' of lymph nodes in the case of immunoblastic lymphadenopathy reported in the Case Records of the Massachusetts General Hospital (1978). In this case a 50-year-old man was diagnosed as IBL with involvement of lymph nodes, tonsils, and bone marrow. Unfortunately, the postmortem examination was restricted to a biopsy of the lung which revealed pneumocystis carinii pneumonia and no

Fig. 8  IBL. Cervical lymph node showing intracytoplasmic immunoglobulin IgG (arrows). Immunoperoxidase x 640.
interstitial infiltrates. Nathwani et al. (1978) have attempted to clarify the clonal evolution of IBL in angioimmunoblastic lymphadenopathy by the demonstration of immunoglobulins by the immunoperoxidase method. In about half of these cases scattered immunoblasts contained kappa or lambda light chains and also the heavy chains. In the rest, only the plasma cells and not the immunoblasts contained immunoglobulins. In cases exhibiting clusters or islands, no immunoglobulins could be demonstrated within these clusters or islands, although scattered immunoblasts in the remainder of the lymph nodes contained immunoglobulins. A decrease in the level of serum immunoglobulins was also observed in seven out of 14 cases of immunoblastic lymphoma arising in angioimmunoblastic lymphadenopathy. These authors suggested that a reduction in the capacity of forming immunoglobulins with resultant hypogammaglobulinaemia was due to replacement of plasma cells and large pyroninophilic cells of angioimmunoblastic lymphadenopathy by neoplastic immunoblastic cells.

Although we were unable to perform ultrastructural and immunological studies on fresh tissues, the presence of intracytoplasmic immunoglobulins in the immunoblasts in the lymph node biopsy specimen and their absence in the neoplastic cells in the lymph nodes obtained at necropsy suggest that the lymphomatous or sarcomatous transformation involved lymphoid cells without any cytoplasmic immunoglobulin. It is possible that the lack of intracytoplasmic immunoglobulins was entirely a postmortem change, or that the neoplastic cells were T-immunoblasts.

Much emphasis has been laid on the proliferation of arborising blood vessels in IBL. These blood vessels are usually numerous in the paracortex and are postcapillary venules (Neiman et al., 1978). The endothelial cells are commonly hypertrophied, and thickening of blood vessels has been attributed to perivascular accumulation of extracellular material.

Necrotising vasculitis of the capsular and pericapsular blood vessels, inflammatory lesions of the intranodal venules and arterioles, and diffuse thrombosis of the small and medium-sized blood vessels should not be considered as the diagnostic
features of IBL. In fact, presence of these features should exclude the diagnosis of IBL (Frizzera et al., 1975). Weisenburger et al. (1977) described four cases of IBL which had pulmonary infiltrates, vasculitis, and hypocomplementaemia. The vasculitis in these cases was extranodal, and its presence along with hypocomplementaemia suggests circulating immune-complexes. Spector and Miller (1977) have described two cases of IBL with pulmonary infiltrates. Similar pulmonary infiltrates were seen in a case reported by Iseman et al. (1976). Positive intracellular fluorescence with antisera to IgG and IgM was present in the alveolar walls of the lung biopsy in this case. In our case there was no radiological infiltration of the lung although the patient had developed a pleural effusion. At necropsy we did not see any immunoblastic pulmonary infiltrates nor was there any evidence of diffuse interstitial pulmonary fibrosis. The significance of pulmonary infiltrates in IBL is not understood. If these infiltrates suggest immune-complex induced injury, similar infiltrates in other organs, especially the kidneys, should be expected.

Ultrastructural studies have shown that the interstitial acidophilic hyaline substance in the lymph nodes is composed of multiple small cytoplasmic components (Palutke et al., 1976) or cell debris resulting from large numbers of dying and degenerating cells (Neiman et al., 1978). The former workers also found depletion of T-lymphocytes in the peripheral blood and tubular cytoplasmic inclusions in the endothelial and lymphoid cells. These tubular cytoplasmic inclusions have been reported in infectious mononucleosis (Moses et al., 1968) and in systemic lupus erythematosus (Haas and Yunis, 1970). Amyloid fibrils have been seen by transmission electron microscopy in the perivascular and interstitial areas in the lymph nodes from two cases of IBL (Madri and Fromowitz, 1978).

Chromosome abnormalities have been detected in IBL. Chromosomally abnormal clones of lymphatic tissue were seen in two cases (Hossfeld et al., 1976), and Volk et al. (1975) reported aneuploidy of numerous pairs in their case of IBL. Since aneuploidy is a common feature of malignant lesions, chromosomal analysis may be helpful in determining the biological nature and evolution of the disease process in IBL.

The management of IBL is difficult especially because of already depressed cell-mediated immunity of the patients and increased susceptibility to infections. Cytotoxic drugs, corticosteroids, and splenectomy have been tried. However, the response, although initially good in some cases, is often short-lived, and frequently the patients develop recurrence or succumb from sepsis.

Levamisole, the immunotrophic drug, has been tried in one case (Bensa et al., 1976). Administration of levamisole was followed by an increase in the numbers of T-lymphocytes in the peripheral blood and conversion of cutaneous anergy to dinitrochlorobenzene. However, the final outcome of this case is not known. Frizzera et al. (1975) have suggested supportive therapy and small doses of steroids.

Perhaps the most important factor in the management of IBL is whether it is allergen-associated or not. In one series consisting of four patients of allergen-associated IBL, single cytotoxic drugs were ineffective but low-dosage prednisone produced complete remission for up to 13 years (Newcomb and Kadin, 1979). In the same study, three cases of non-allergen associated IBL did not respond to prednisone but combination chemotherapy resulted in remission. Until we know more about IBL, this regime seems to be a logical therapeutic approach.

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