Angiofollicular lymph node hyperplasia with amyloidosis

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Summary: Two cases of angiofollicular lymph node hyperplasia are described, one of the solitary plasma cell type the other of the multicentric hyaline vascular type.

Both cases illustrate the wide ranging clinical and pathological findings associated with this condition but both also have unusual features. The solitary plasma cell lesion had an exceptional 32 year clinical history and was associated with systemic amyloidosis of AL type. The multicentric hyaline vascular case was associated with coexistent multiple myeloma and amyloid deposition also of AL type. These cases are presented with a review of the relevant literature.

Introduction

Angiofollicular lymph node hyperplasia (AFLNH) was first described in 1956.¹ It was originally reported as a solitary mediastinal lesion but it has since been described in other sites.² Multicentric involvement has also been reported.^{3,4}

AFLNH has been divided into two clinico-pathological variants, the hyaline vascular type and the plasma cell type.⁵ The plasma cell type is less common and consists of hyalinization or hyperplasia of lymphoid follicles separated by sheets of plasma cells. There are frequent systemic manifestations including fever, anaemia and hypergammaglobulinaemia. These abate when the lesion is removed. The hyaline vascular type is characterized by small follicles with radially penetrating vessels separated by richly vascular interfollicular tissue. Transitional forms of AFLNH have also been described.⁵

The multicentric form of the disease frequently has systemic manifestations and runs an aggressive clinical course with a fatal outcome.^{3,4,6} Furthermore, these patients run an increased risk of developing Kaposi's sarcoma and malignant lymphoma.⁴

We describe two cases of AFLNH, one solitary and one multicentric, that together demonstrate the broad histological and clinical spectrum of the disease.

Case reports

Case 1

A 55 year old Caucasian woman presented complaining of nausea, vomiting and chest pain. She had a past

history of an anterior mediastinal mass present on chest X-ray for 32 years. The presence of this mass was subsequently confirmed by computerized tomography. Examination revealed complete heart block, cardiomegaly and hepatomegaly. Laboratory investigations were as follows: haemoglobin 9.8 g/l, ESR 140 mm/h, potassium 6.1 mmol/l, urea 23.5 mmol/l, creatinine 582 µmol/l, albumin 30 g/l, serum immunoglobulin: IgG 25.7 g/l, IgM 2.88 g/l, IgA 3.50 g/l. No serum paraprotein was identified and there were no Bence Jones proteins in the urine. A bone marrow biopsy contained 5% plasma cells. The patient was referred for biopsy of her mediastinal mass and died suddenly 24 hours after surgery.

At autopsy a mass 6 × 4 × 4 cm was identified in the anterior mediastinum adjacent to the superior vena cava. This had a haemorrhagic cut surface with flecks of calcification. The heart weighed 450 g, the myocardium was pale and both ventricles were thickened. The kidneys each weighed 100 g, had pale waxy cortices and pitted subcapsular surfaces. There was no other lymphadenopathy.

Microscopy of the mediastinal mass revealed lymphoid tissue in which small aggregates of lymphocytes were surrounded by sheets of plasma cells, some of which appeared bizarre and binucleate. Immunoperoxidase staining for immunoglobulin light chains showed that these cells were polyclonal. These appearances were considered to represent the plasma cell variant of AFLNH. Lymph nodes elsewhere were unaffected.

Examination of the kidneys and heart revealed the presence of amyloid stainable by Congo Red. Amyloid was also demonstrable on electron microscopy. Using potassium permanganate pretreatment the amyloid was found to be of AL type. Immunoglobulin light

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Figure 1 Case 2: follicle showing hyalinization and layering of small lymphoid cells (H & E $\times$ 250).

chains could not, however, be demonstrated in the tissue available.⁷

Case 2

A 57 year old Caucasian male presented complaining of chest pain and weight loss of 7 kg in a 9 month period. Examination revealed right cervical and axillary lymphadenopathy and hepatosplenomegaly. Investigations were as follows: haemoglobin 13.9 g/dl, plasma viscosity 1.67 cP, potassium 5.0 mmol/l, urea 10.6 mmol/l, creatinine 139 μ mol/l, albumin 29 g/l. Plasma electrophoresis revealed a monoclonal IgA lambda band. Radiological examination demonstrated osteosclerotic lesions in vertebrae and ribs but no mediastinal mass was identified. A liver biopsy and vertebral biopsy were normal but axillary lymph node biopsy showed AFLNH of the hyaline vascular type (Figure 1).

Treatment with prednisolone was commenced but the patient continued to lose weight and was readmitted with papilloedema, neuropathy and a chest infection. Investigation at this time showed plasma sodium 119 mmol/l, potassium 8.1 mmol/l, urea 40 mmol/l, creatinine 212 μ mol/l. Cerebrospinal fluid was sampled and the findings were consistent with Guillain-Barré syndrome. The hyperkalaemia was treated with calcium-resonium and the chest infection with

antibiotics. The neuropathy and papilloedema resolved spontaneously but there was a general deterioration with the development of profound hypoproteinaemia (albumin 19 g/l) and associated oedema, ascites and pleural effusions. The patient died 10 months after the initial presentation.

At autopsy enlarged lymph nodes up to 3.5 cm in diameter were found in the mediastinum, pulmonary hila, paratracheal, para-aortic and inguinal regions. The spleen weighed 490 g and had a uniform deep red cut surface. Hard pale osteosclerotic lesions were identified in the 12th thoracic and 1st lumbar vertebrae and softer pale nodules 3 cm across were identified in the 10th and 11th ribs on the right. Ascites, pericardial and pleural effusions were noted and there was marked pulmonary oedema.

Histological examination of lymph node biopsies from this patient showed the typical features of the hyaline vascular variant of AFLNH. Numerous small follicles were present, many with hyaline centres and radially penetrating vessels. The interfollicular tissue was highly vascular but plasma cells were not conspicuous.

Histological examination of lymph nodes from all sites at autopsy revealed marked autolysis but their appearances were consistent with AFLNH of hyaline vascular subtype. The spleen was histologically normal.

The bone marrow contained a monoclonal IgA

Figure 2 Case 2: nodule of amyloid from a rib including multinucleate giant cells (H & E $\times$ 250).

lambda plasma cell proliferation in keeping with the patient's circulating paraprotein.

The osteosclerotic lesions consisted of thickened bony trabeculae which appeared similar to those of Paget's disease with prominent cement lines. The residual marrow spaces contained abundant plasma cells. The nodular lesions from the ribs consisted of large amounts of amyloid with associated multinucleate giant cells (Figure 2). This was found to be of AL type and stained positively for lambda light chain.

Discussion

The cases described exemplify the spectrum of clinical and pathological findings in AFLNH.

Case 1 is an example of the solitary plasma cell variant of the disease. This accounts for less than 10% of cases⁵ and it is often associated with a polyclonal hyperglobulinaemia and anaemia⁸ both of which were present in the case described. The apparent 32-year history in this case is, however, unusual.

The presence of amyloidosis in association with AFLNH is a rare but documented finding.⁹⁻¹¹ One of the previous cases⁸ was of a mixed plasma cell and hyaline vascular type and the amyloid deposition was confined to the lesion itself and the spleen. The other two cases^{10,11} were of the solitary plasma cell type and in both there was systemic amyloidosis in association with nephrotic syndrome.

The origin of the amyloid material in AFLNH has been the subject of some discussion in the literature. Bonneau *et al.*⁹ and Chan *et al.*¹¹ thought that it was of so called AA type. This is the form of amyloid seen in chronic reactive states and the fibrils are derived from serum amyloid A.¹² Garcia-San Miguel *et al.*,¹⁰ however, found amyloid of AL type in a case of AFLNH and it is this type of amyloid that was present in both of our cases. In AL amyloid the fibrils are derived from modified immunoglobulin light chains.¹² Both of our patients had a source of excessive immunoglobulin production. Patient 1 had a polyclonal hyperglobulinaemia at the time of investigation and this may have been present for up to 32 years. The patient had no other demonstrable condition known to be associated with amyloidosis and its development appears to have been related to her AFLNH.

Case 2 is an example of the hyaline vascular type of AFLNH. This is the more common histological type but is uncommonly multicentric.⁸ Furthermore the associated manifestations in our case were more severe than those usually seen in hyaline vascular AFLNH. Weissenberger *et al.*⁴ studied 16 cases of multicentric AFLNH of which five were wholly or partly of the hyaline vascular type. All of these, in common with our case, had lymphadenopathy and one also had splenomegaly. Three complained of weight loss. One

of their cases developed transient renal failure which was also noted in our case. Gaba *et al.*³ reported a single case of AFLNH of hyaline vascular type associated with peripheral neuropathy affecting particularly the lower limbs. A similar neuropathy was evident in case 2. Recently¹³ a case of pseudotumour cerebri has been reported in association with AFLNH in which transient papilloedema was seen. Papilloedema was also seen in case 2.¹³

Patient 2 also had amyloidosis but was suffering from multiple myeloma and this, rather than AFLNH, may have been the underlying cause. It is interesting to note that the patient was producing a lambda paraprotein since lambda light chains are more commonly associated with amyloid deposition than are kappa light chains.¹² Amyloidosis in conjunction with multiple myeloma is recognized as having an unusual distribution in comparison to other types. In particular tumorous deposits of amyloid in bone are well recognized.¹⁴

The association of myeloma and AFLNH is also unusual. Although lymphomas have been recorded the plasma cell population in AFLNH is usually polyclonal. However, one group have described three cases with monoclonal plasma cell proliferations and one of these had a detectable paraprotein in the serum.¹⁵ Furthermore the association of gamma heavy chain disease and AFLNH has been demonstrated in a patient with impaired T cell function.¹⁶

Bardwick *et al.*¹⁷ described the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) in which lymphadenopathy due to AFLNH is seen usually in association with the osteosclerotic type of multiple myeloma. Case certainly showed clinical evidence of polyneuropathy and a paraprotein and osteosclerotic lesions were present in association with myeloma. However, in this case the AFLNH was of hyaline vascular type whereas in other cases reported it has been of the plasma cell type.¹⁸

These cases represent two ends of a broad spectrum of disease that may be localized or multifocal in nature. In addition they provide an insight into some of the more unusual associations of this condition. Concerning the underlying cause of AFLNH the present cases are unable to throw further light on the suggestion of an association with immune deficiency states. Clearly there is much to be learnt by this long-term follow-up of AFLNH of all types in order to unravel the underlying histogenesis and pathogenesis of the condition.

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