Virchows Arch (1999) 434:259–262

CASE REPORT

C. Ibarrola de Andrés · R. Toscano · J.J. Lahuerta
M.A. Martínez-González

Simultaneous occurrence of Hodgkin's disease, nodal Langerhans' cell histiocytosis and multiple myeloma IgA(κ)

Received: 15 April 1998 / Accepted: 20 September 1998

Abstract A 35-year-old man suffered simultaneously from nodular sclerosis Hodgkin's disease (HD), Langerhans' cell histiocytosis and multiple myeloma (MM). There was no prior history of irradiation or chemotherapy, and clinically the lymphoma was confined to cervical lymph nodes. Immunohistochemically, neoplastic lymphoma cells reacted with CD15 and CD30 markers. The patient's bone marrow exhibited a diffuse infiltration by rather atypical plasma cells showing κ immunoglobulin light-chain restriction. At 14 months after the diagnosis, after autologous bone marrow transplantation, the clinical evolution is favourable with complete remission of the diseases. This is the first time that the coexistence of these three haematological disorders has been discussed, and only the fourth documented case of simultaneous HD and MM. Speculations about the significance of this finding are discussed.

Key words Hodgkin's disease · Myeloma · Langerhans' cell histiocytosis · Discordant lymphoma · Lymph node

Introduction

In 1950 Greenberg reported the first occurrence of Hodgkin's disease (HD) and multiple myeloma (MM) [11]. Only five other similar cases have been described in the literature [1–3, 14, 24], with a simultaneous diagnosis of both diseases occurring in only three of these [2, 14, 24]. The purpose of this paper is to present a new case in which, in addition, an isolated node showed Langerhans' cell histiocytosis (LCH). The association of these three haematological disorders has not been reported before.

C. Ibarrola de Andrés (✉)[1] · M.A. Martínez-González
R. Toscano · J.J. Lahuerta
Department of Pathology, Hospital 12 de Octubre', Madrid, Spain

Present address:
[1] Department of Haematology, Hospital 12 de Octubre', Madrid, Spain

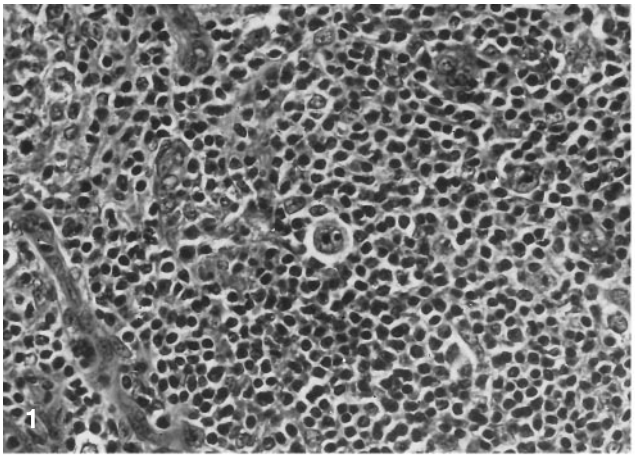
Mailing address:
C. Ibarrola de Andrés, C/Mercedes de la Cadiniere nº42, Pozuelo de Alarcón, E-28223 Madrid, Spain
Tel.: +34-1-3908275

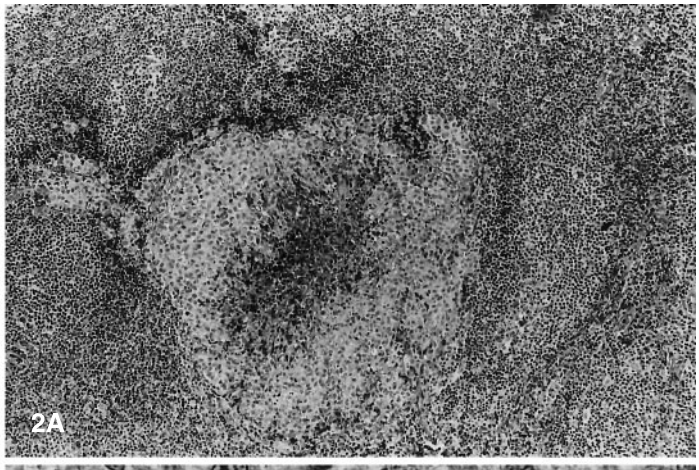
Case report

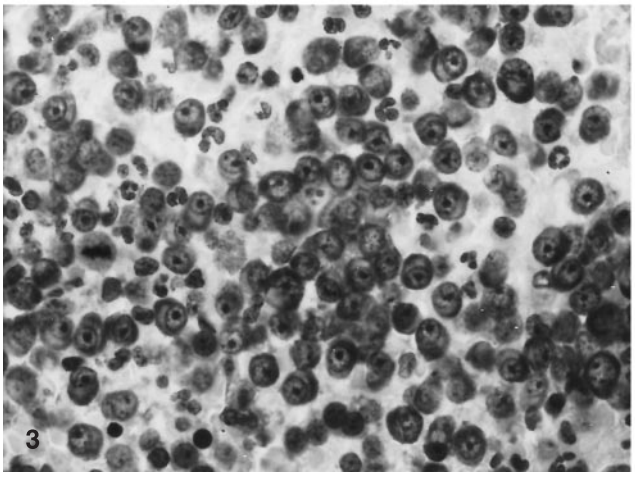
A 37-year-old man presented with a right cervical tumour discovered by himself 6 months before, which meanwhile measured 10×8 cm. The patient complained of fatigue and loss of appetite. After cervical lymph node biopsy, the histological diagnosis made was type I nodular sclerosis HD with a LCH focus in an affected node. At this time serum electrophoresis showed an IgA (κ) paraprotein of 3200 mg% and a beta-2 microglobulin level of 7.6 ng/l. Free κ immunoglobulin light-chains were detected in the urine. X-ray films of the skeleton showed osteolytic lesions in the calvarium, ribs, dorsolumbar part of the vertebral column, pelvis and both femoral metaphyses. A computed tomographic scan revealed enlarged bilateral cervical lymph nodes without enlarged liver, spleen, or other lymph nodes. Bone marrow examination showed extensive infiltration by atypical plasma cells. The final diagnosis was MM without evidence of bone marrow HD infiltration. Treatment with three cycles of ABVD resulted in complete remission of HD. The patient was then given cyclophosphamide and C-SFG to obtain haematopoietic stem cells. Five months after diagnosis an autologous bone marrow transplantation (following prior therapy with 200 mg/m^2 of melphalan) was performed. A second autologous transplantion (following prior therapy with cyclophosphamide, carmustine and etoposide) was done 6 months later. The patient continues in complete clinical remission of his HD and shows slight bone marrow hypocellularity, without plasma cell infiltration, 14 months from the initial diagnosis. Paraproteinaemia has also disappeared.

Materials and methods

Lymph node and bone marrow biopsy specimens were examined in paraffin sections stained with either haematoxylin and eosin or Wright-Giemsa. Lymph node samples were fixed with formalin, and the bone marrow sample was fixed in 4% buffered formaldehyde for 3 h and then decalcified in 2% acetic acid for 24 h. Paraffin sections were subjected to immunohistochemistry using the avidin–biotin complex method of Hsu et al. [13]. Antigen retrieval was performed in a pressure cooker. The slides were washed in citrate buffer (pH 6.0). The antibody panel included LCA (CD45, 1:50, Dako), L26 (CD20, 1:200, Dako), CD43 (CD43,1:200,







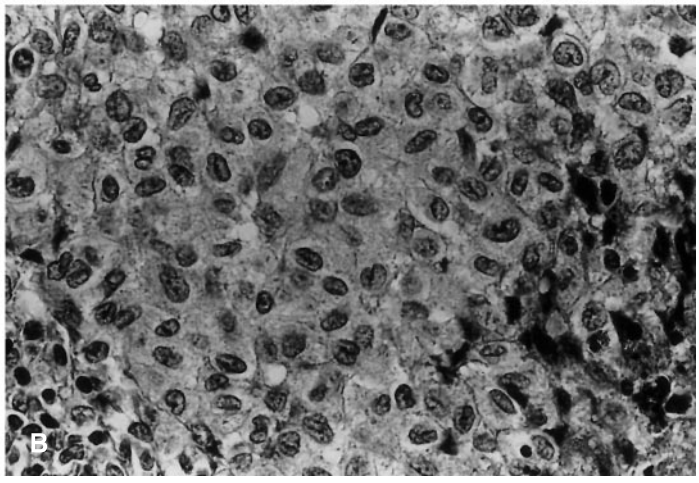


Fig. 1 Detail of the cervical lymph node specimen with an occasional Reed-Sternberg cell noted among lymphoid cells. Haematoxylin and eosin, ×250

Fig. 2 **A** Low-magnification view of packed Langerhans' cells surrounding a collection of eosinophils with central necrosis. **B** At higher magnification their characteristic indented nucleus and their ample and clear cytoplasm can be appreciated. Haematoxylin and eosin stain, **A** ×200. **B** ×940

Fig. 3 Bone marrow shows numerous plasma cells with large nucleus and prominent centrally located nucleolus. Note the presence of mitoses. Wright-Giemsa, ×940

Dako), UCHL1 (CD45RO, 1:100, Dako), LeuM1 (CD15, 1:10 Becton Dickinson), BerH2 (CD30, 1:50, Dako), LMP-1 for EBV (1:50, Dako), EMA (1:100, Dako), S-100 protein (1:1000, Dako), CD1a (1:1, Immunotech, Marseille, France), κ (1:2000, Dako) and λ (1:2000, Dako) immunoglobulin light-chains.

Pathological findings

Lymph node biopsy consisted in the study of two removed cervical lymph nodes each measuring 3×2×1 cm. Histologically, they showed effacement of their primitive architecture, which was substituted by lymphoid nodules, partly bordered by collagen bands and composed of mature lymphocytes intermingled with eosinophils, histiocytes, and lacunar-type Reed-Sternberg (RS) cells. Only a few classic RS cells were observed (Fig. 1). Classic and lacunar RS cells reacted with CD15 and CD30 and were negative with CD45, CD20, CD43, CD45RO, EMA and LMP–1. There were some polytypic plasma cells with a normal morphology dispersed throughout the nodes. One of these nodes showed a single focus of cells with a histiocytic appearance, vesicular nuclei, folded and grooved nuclear membranes, inconspicuous nucleoli, and a fairly pale and abundant cytoplasm (Fig. 2A, B). An intense cytoplasmic reactivity for S-100 antibody and membranous possitivity for CD1a antibody confirmed the diagnosis of Langerhans' cells. This cluster of cells surrounded a large aggregation of eosinophils with central necrosis. Bone marrow aspirate yielded only blood. The biopsy revealed diffuse and extensive infiltration by plasma cells. They showed a range from moderate to severe atypia, with a noncentred vesicular nucleus, a large central nucleolus and a moderate basophilic cytoplasm (Fig. 3). Mitotic figures were observed. Plasma cells were accompanied by a nonspecific lymphoid infiltrate and a moderate deposition of reticulin. A smear of the biopsy material confirmed the presence of numerous plasmablasts. Plasma cells expressed a monotypic pattern of reactivity with κ immunoglobulin light-chain.

Discussion

The existence of composite and discordant lymphomas appearing either simultaneously or sequentially is well recognized [6, 19]. The most important manifestations of this phenomenon in "classic" HD are its combination with chronic lymphocytic leukaemia [27], peripheral postthymic T-cell lymphoma [4, 12], and large cell lymphoma of the B-cell type [15, 29, 30]. The association of HD with plasma cell dyscrasias is rare. To our knowledge no cases with MM preceding HD have been reported. Some patients have developed plasmocytoma [10, 20], MM [1, 3, 11] or monotypic plasma cell proliferations of unknown significance [9] after HD therapy These proliferations were attributed to the carcinogenic risks associated with the therapy. There have been also some reports of simultaneous occurrence of HD and paraproteinaemia of uncertain significance [5, 16, 26, 28], including one of a case with bone marrow plasmocytosis [26] and another with monotypic plasma cell proliferation in a lymph node [28]. As far as we know the diagnosis of HD and MM occurring concurrently has previously been made in only three cases [2, 14, 24]. These cases were described in two men 51 and 60 years of age, and a woman of 78, with diverse clinical stages and different subtypes of HD at the time of diagnosis. Two patients showed bone marrow infiltration by HD and MM at the same time [14, 24]. One of the patients, who was treated with MOPP (4 cycles), bleomycin, and prednisone (after a relapse) was in complete clinical remission 2 years after the diagnosis [24]. The other two died, one of them at the time of diagnosis [14] and the other of unknown cause cause local radiotherapy [2].

The significance of the HD-MM association remains unknown. There is evidence to suggest that some cases of HD may be of B-cell origin [25]. In light of this, the two neoplasms could represent different stages in the evolution of a single malignant clone of cells. The malignant HD cells could be the result of a maturation arrest of the B-cell series, and on the other hand, the neoplasm of plasma cells could be the result of a complete differentiation of these cells [14]. Depressed cell-mediated immunity in HD can also explain the development of other neoplasms including MM. In addition, known and unknown factors could have a role in the pathogenesis of both processes. Finally, occurrence of HD and MM concurrently might be a mere coincidence, but the patient presented was only 35 years old, an age at which MM has rarely been reported.

It seems that the association of LCH with malignant lymphomas occurs more often than could be expected by chance, HD being the lymphoma most frequently associated with LCH [7]. Up to 1997, approximately 30 patients with a diagnosis of LCH and HD had been reported [7, 21]. Most frequently, the HD either preceded LCH (11 cases) or was diagnosed at the same time (17 cases) [7, 8, 17]. In 15 of the latter cases, including ours, LCH appeared in draining lymph nodes of the lymphoma. Infiltration by Langerhans' cells took the form of localized foci and/or of extensive multifocal involvement within dilated cortical and medullary sinuses [23], with no evidence of a posterior systemic spread [7, 21]. It seems that nodal LCH represents a process with a benign clinical course, as demonstrated in the literature [7, 22]. This is, however, a curious event if we consider the old-fashioned hypothesis of a malignant change in cells of the monocyte–histiocyte system as the origin of the "classic" HD [18]. In the present case, as in the previously reported cases, there was no histological evidence of conversion of one lesion into the other. To summarize, we report the unusual coexistence of three haematological disorders, but the significance of this association remains unknown.

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