Non-secretory multiple myeloma presenting as primary plasma cell leukaemia

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Summary: A case of non-secretory multiple myeloma presenting as primary plasma cell leukaemia in a 65 year old woman is presented. Bone pain was the initial clinical manifestation. Laboratory analysis showed 20% of circulating immature plasma cells. Despite the presence of osteolytic lesions, no M-component could be demonstrated in serum protein electrophoresis, and serum and urine immunoelectrophoresis. Bone marrow aspirate demonstrated an 83% infiltration of plasma cells showing various degrees of immaturity. Immunofluorescence with monoclonal antisera demonstrated intracytoplasmic kappa light chains in a high percentage of plasma cells. Immature plasma cells without cellular capacity to synthesize and excrete complete immunoglobulins could be more aggressive, leading to an initial leukaemic process. Previous work regarding possible pathogenetic mechanisms, clinical and laboratory features, and response to treatment of this extremely rare association are reviewed.

Introduction

Non-secretory multiple myeloma (MM), characterized by the absence of detectable heavy or light chains in the serum and urine, is rare, constituting an estimated 1–4% of all MM cases.¹ Plasma cell leukaemia (PCL) is a malignant plasma cell dyscrasia due to proliferation of these cells in the bone marrow, peripheral blood and visceral organs with an incidence of 1.6–2% that of MM.² Only a few well-documented cases of non-secretory MM presenting as primary PCL have been reported.^{3–7}

The case history of a patient with concomitant non-secretory MM and primary PCL is presented, and the literature on clinical features and response to chemotherapy of this exceedingly rare association is reviewed.

Case report

A 65 year old woman was admitted because of increasing bone pain, which started 20 days prior to admission in the left shoulder and ribs. Clinical examination was unremarkable except for tenderness on the anterior arches from fifth and sixth left ribs. Laboratory studies disclosed erythrocyte sedimentation rate 65 mm per hour, haemoglobin

8.3 g/dl, mean corpuscular volume 93 fl and platelet count $140 \times 10^9/l$. White cell count was $13.2 \times 10^9/l$ with 20% immature plasma cells. In the peripheral blood smear, rouleaux, marked anisocytosis and 6% circulating erythroblasts were observed. Serum creatinine was 124 $\mu\text{mol/l}$, uric acid 524 $\mu\text{mol/l}$, serum calcium 2.62 mmol/l and serum phosphate 2.13 mmol/l. Total protein was 49.4 g/l. Immunoelectrophoresis of serum with oligo- and monospecific antisera showed markedly decreased levels of IgG, IgA and IgM: 3, 0.34 and 0.24 g/l, respectively. Immunoelectrophoresis of the urine concentrated 100-fold failed to demonstrate light chains. Bone X-ray showed osteolytic punched-out lesions in the skull, left humerus, left clavicle and anterior arch of fifth and sixth left ribs. A compression fracture of the first lumbar vertebra was observed.

Bone marrow aspirate-biopsy disclosed a hypercellular marrow with an infiltration of 83% by plasma cells of different sizes, with immature features, some of them binucleated. Occasional mitoses could be seen. Examination of the marrow using fluorescein-conjugated antisera specific for each of the immunoglobulin heavy chains and for kappa and lambda light chains showed that the vast majority of plasma cells contained kappa chains in their cytoplasm.

The patient was diagnosed as having non-secretory MM presenting as primary PCL and treatment with combination chemotherapy (M2 protocol: cyclophosphamide 400 mg/m² i.v. $\times$ 1,

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vincristine 1.2 mg/m² i.v. × 1, BCNU 20 mg/m² i.v. × 1, melphalan 10 mg/m² p.o. × 4 and prednisone 40 mg/m² p.o. × 4) was initiated. The response was excellent with complete clearance of plasma cells from the peripheral blood within the first 4 days of treatment. She continues to receive cyclic chemotherapy and is in complete remission with a follow-up of 4 months.

Discussion

Non-secretory MM was described more than 20 years ago⁸ and is characterized by the absence of an M-component in serum and urine. It represents less than 1% of all the patients diagnosed of having MM.^{1,9,10} PCL probably represents one of the rarest forms of acute leukaemia occurring in up to 5% of the patients with plasmatic dyscrasias.^{2,11,12} The diagnosis is usually established by the demonstration of circulating plasma cells in numbers either >20% of the total white-cell count or >0.2 × 10⁹/l.^{11,12} PCL can occur as a terminal event in the evolution of MM (secondary PCL) or as a presenting feature, in a patient with no previous history of plasma cell dyscrasia (primary PCL).

The coexistence of non-secretory MM and primary PCL in the same patient is of clinical interest. To the best of our knowledge, this association has only been described in six other individuals. Bone pain was present as the initial clinical symptom in six out of seven patients, four of whom were female. Osteolytic lesions, reported to be more frequent in secondary than in primary PCL,^{13,14} were observed in 70% of the patients. Organomegaly was not as frequent as in PCL^{11,14} only 28% of the patients had hepatomegaly at diagnosis and none had splenomegaly or peripheral lymphadenopathy. Mild to moderate anaemia was present in four out of six patients. Serum calcium and creatinine were within normal limits in all but one patient, renal function impairment appears to be less frequent in non-secretory MM than in the secretory type.^{6,15} Hypogammaglobulinemia occurred in most of the seven patients reviewed. This fact is in accordance with some authors,^{6,16,17} although others have found

normal polyclonal immunoglobulin levels.¹⁰ Chemotherapy regimens varied from one patient to another.

Response to treatment was generally poor with three of the seven patients reaching a complete remission and survival short: four patients died within the first 45 days from diagnosis. Survival was not related to treatment received. There are conflicting opinions on the evolution and clinical response of MM with no M-component: although a bad prognosis was first reported,^{16,18} in recent reports there was no significant difference between the non-secretory and the secretory type of MM^{17,19} and even a better prognosis could be supposed on the basis of a spared renal function.^{9,17,20} On the other hand, primary PCL is an aggressive disease considered to have developed from the most immature plasma cells: median survival of these patients is generally short (range 2–6.8 months) with poor response to the chemotherapy administered.^{2,5,7,11,12,21}

Non-secretory MM can be difficult to diagnose and distinguish from carcinomatous infiltration of the bone marrow in elderly patients with skeletal disseminated lytic lesions²² sometimes leading to erroneous initial diagnosis.²³ With the improvement of diagnostic tools, it has been possible to demonstrate two different situations in MM with no M-component: (1) patients with positive immunofluorescence in plasma cells (secretory non-excretory MM)^{5,6,9,16,18,20,24} and (2) patients with negative immunofluorescence (true non-secretory MM).^{9,18,23,25} The patient we present has to be included in the first group with the demonstration of intracytoplasmic kappa chains with monospecific antisera immunofluorescence. The diagnosis of primary PCL may also be difficult when the predominant plasma cells are immature or when there are few morphological features of plasma cell differentiation.^{7,21,26} In these cases, an erroneous diagnosis of undifferentiated acute leukaemia or another form of lymphoproliferative disease can be raised.^{7,21} In our case, the demonstration of monoclonality in plasma cells allowed us to make a prompt diagnosis but the use of transmission electron microscopy in order to extensively study plasma cells is advised.^{4–6,21,27}

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