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Multiple myeloma associated to Biermer's disease

Abstract

Introduction: The association of Biermer's disease or pernicious anemia (PA) with multiple myeloma (MM), still characterized as unusual, is a true diagnostic and therapeutic challenge for the clinician and underlines the particular carcinogenicity of pernicious anemia. We report a case.

Observation: A 75-year-old Tunisian man with no medical history, was admitted to our clinic for evaluation of a bicytopenia: anemia (hemoglobin at 7.8g/dl) with macrocytosis (MCV=109µ^3), and thrombocytopenia 58,000/mm^3. The diagnosis of PA was made (vitamin B12 deficiency, positive anti-intrinsic factor antibodies, and positive anti-parietal cell antibodies) and the patient put under Vitamins B12 intramuscularly at a dose of 1000µg/d. Erythrocyte count control after ten days of vitamin therapy did not show reticulocyte crisis. The myelogram was then performed objectifying, in addition to signs of PA, asignificant plasma cell infiltration estimated at 55% made of dystrophic plasma cells. The plasma protein electrophoresis, urine tests and radiological assessment had concluded to stage IIIA IgG kappa MM associated with the PA. The patient was transferred to hematology department for adapted therapeutic management.

Conclusion: As rare as it is, this association deserves to be known given its therapeutic and prognostic implications. Screening for a monoclonal immunoglobulin seems useful prior to initiation of treatment with vitamin B12 during PA.

Keywords: biermer's disease, multiple myeloma, pernicious anemia, monoclonal gammopathy

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Introduction

Since the first observation by Larsson SO in 1962,[1] the association of pernicious anemia (PA), or Biermer's disease, with multiple myeloma (MM) has been rarely reported: only about thirty cases have been found in the world literature, in the form of sporadic cases.[2–4] This association, still considered unusual,[3,4] represents a real diagnostic and therapeutic challenge for clinicians and highlights the particularly carcinogenic nature of Biermer's disease.[5,6] We report a case of Biermer's disease associated with IgG kappa MM, illustrating the diagnostic and therapeutic difficulties of this exceptional association.

Case presentation

A 75-year-old Tunisian man with no prior medical history was admitted to our department for investigation of bicytopenia. His illness began three months prior to hospitalization with the onset of asthenia and occasional episodes of dizziness, prompting him to consult his family doctor. His initial blood count showed normochromic normocytic anemia with hemoglobin at 8.5 g/dL. The patient was referred to a gastroenterologist who ordered an abdominal ultrasound, upper endoscopy, colonoscopy, and a thoracoabdominal CT scan, all of which were normal. The patient was started on iron therapy (Tardyferon® 50 mg, 2 tablets daily) but without improvement.

The follow-up assessment after one month revealed persistent anemia (hemoglobin at 7.8 g/dL) with macrocytosis (MCV at 109µm^3) and thrombocytopenia (platelets at 58,000/mm^3). The patient was referred to us for etiological investigation of this bicytopenia. The physical examination was unremarkable except for marked pallor of the skin and conjunctiva, and diffuse hyperreflexia. In particular, no palpable peripheral lymphadenopathy or visceromegaly was noted. The patient was afebrile and had no progressive skin lesions.

Laboratory tests confirmed the bicytopenia and revealed an inflammatory syndrome with an erythrocyte sedimentation rate of 120 mmH1 and a protein-reactive protein level of 20 mg/L. Liver function tests, serum calcium, renal function, blood glucose, and muscle enzymes were normal. Thyroid function was normal (free thyroxine at 14 pmol/L and thyroid-stimulating hormone at 4.2 µIU/mL). Vitamin B12 levels were severely deficient at 30 pmol/L (normal range of 141–489 pmol/L). Folic acid levels were normal at 38 mmol/L. Immunological testing revealed positive anti-intrinsic factor antibodies at 180 (normal range <1.20) and positive anti-parietal cell antibodies at 160 (normal range <40). A diagnosis of PA was therefore made, and the patient was started on intramuscular vitamin B12 at a dose of 1000 µg/day. A follow-up red blood cell count after ten days of vitamin therapy showed no evidence of a reticulocyte crisis. A myelogram was then performed, revealing, in addition to signs of PA (megaloblastosis with asynchronous nucleocytoplasmic maturation and a slight block in granulocyte maturation with polysegmented nuclei), a significant plasmacytic infiltration estimated at 55%, composed of dystrophic plasma cells (Figure 1 and 2).

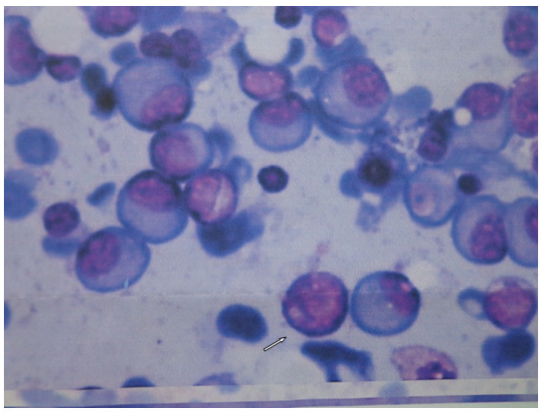

Figure 1 Myelogram showing excess plasma cells with megaloblastosis (arrow).

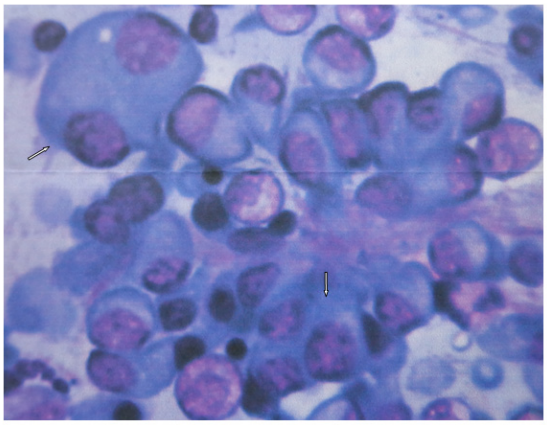

Figure 2 Myelogram showing the dystrophic nature of the plasma cells (arrows).

Plasma protein electrophoresis showed a monoclonal spike in gamma-globulin region at 39 g/L with suppression of other proteins. Immunoelectrophoresis identified a monoclonal IgG immunoglobulin with a kappa light chain. Radiological examination (skull, long bones, ribs, pelvis, thoracolumbar spine, as well as the initial thoracoabdominal CT scan) revealed only a few well-defined geodic lesions in the skull. Following this assessment, a diagnosis of stage IIIA IgG kappa MM associated with PA was made, and the patient was transferred to the hematology department for appropriate therapeutic management.

Discussion

It has long been known that minimal megaloblastosis, described as "insignificant," can be seen in almost a third of myeloma patients, and that in 19%, this megaloblastosis may be moderate; however, it does not cause overt anemia.[7] These morphological abnormalities are related to a relative deficiency in folic acid and/or vitamin B12.[7,8] The occurrence of megaloblastic anemia in multiple myeloma remains rare, and that of authentic pernicious anemia is exceptional.[2–4,9–12] The pathogenesis of this association is not yet well understood. Initially, it was thought that because the majority of myeloma patients are elderly, hypo- or achlorhydria is common in these individuals, explaining the anemias and/or megaloblastosis observed in multiple myeloma.[8]

However, this explanation alone appears insufficient to account for all megaloblastosis cases occurring in myeloma patients, since the association between multiple myeloma and pernicious anemia has also been reported in very young individuals in their thirties.[4,11] Recently, it has been demonstrated that the uptake and consumption of cobalamin by myeloma cells are significantly higher compared to those of normal bone marrow cells; similarly, this cobalamin appears to be necessary for the synthesis of the monoclonal immunoglobulin in multiple myeloma.[8] The description of the association of pernicious anemia with non-secretory multiple myeloma[11] rather reinforces the hypothesis of a secondary vitamin B12 deficiency induced by the uncontrolled development of pathological plasma cells.[7,8,11] In rare cases, megaloblastic anemia in multiple myeloma can result from vitamin B12 malabsorption secondary to myeloma infiltration of the gastrointestinal tract, leading to damage or destruction of gastric parietal cells, as illustrated by the observation of Doberauer C et al.[13]

The association of authentic pernicious anemia of immunological origin (Biermer's disease) with positive autoantibodies against intrinsic factor and/or parietal cells in multiple myeloma remains an unresolved mechanism.[2,3,11] This association, even if its pathogenic mechanisms have not yet been demonstrated, is far from random and appears to be bidirectional:- Indeed, the large Swedish study, which included 8,406 subjects with MM diagnosed and followed between 1958 and 1998, showed a significantly higher risk of developing PA in myeloma patients compared to matched healthy controls, with an odds ratio (OR) of 3.27,[14] and some authors even estimate that the prevalence of PA is multiplied by 10 in cases of underlying MM.[15]

Conversely, the presence of PA exposes patients to a higher subsequent risk of developing solid tumors and/or hematological malignancies, including MM. The standardized incidence rate (SIR) of which was 2.1 to 2.5 compared to the matched general population.[5,6] This incidence was particularly higher in women.[5] This association also poses a problem in the therapeutic management of these patients, since MM can be triggered or exacerbated by the initiation of vitamin therapy for PA due to the "beneficial" effect of cobalamin on the growth of myeloma cells.[11,16] Indeed, this vitamin acts as a paracrine growth factor for plasma cells and also contributes to osteolytic activity,[16] explaining why the presence of MM is an aggravating factor in the clinical course of PA, often with a fatal outcome.[3,4] Therefore, several authors suggest measuring vitamin B12 levels in all patients with MM or monoclonal gammopathy, as well as testing for a paraprotein in all patients with PA.[17]

Conclusion

However rare, this association deserves to be recognized given its therapeutic and prognostic implications. Screening for a monoclonal immunoglobulin appears useful before initiating vitamin B12 treatment in the context of pernicious anemia.

Acknowledgments

None.

Conflicts of interest

None.

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