Generalized cutis laxa and fibrillar glomerulopathy resulting from IgG Deposition in IgG-lambda Monoclonal Gammopathy: pulmonary hemorrhage during stem cell mobilization and complete hematological response with bortezomib and dexamethasone therapy

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Background

Cutis laxa (CL) is an exceedingly rare inherited or acquired skin disorder resulting from alterations in the elastic fibers of the skin (1) The clinical picture consists of an inelastic skin, that looks loose and pendulous predominantly in body fold areas of the axilla, groin or neck (2). This gives a picture of ‘premature ageing’ that will usually be the main patient complain. This syndrome, in its acquired form, has been associated with many etiologies, such as penicillamine and isoniazid administration (3, 4), Borrelia infections (5), celiac disease (6) or systemic lupus erythematosus (7). In a few cases, it has been reported in association with multiple myeloma, as well as with B and T cell lymphomas (1, 2, 8, 9). Herein, the case of patient with acquired generalized CL associated with IgG-lambda monoclonal gammopathy who also presented a fibrillar glomerulopathy (resulting from IgG-deposition) rapidly evolving to renal failure is reported. A severe pulmonary hemorrhage developed during stem cells mobilization with granulocyte colony-stimulating factor (G-CSF). The patient subsequently achieved a hematological complete response with bortezomib and dexamethasone therapy. To our knowledge this is the first report of a patient with generalized acquired CL complicated by G-CSF-induced pulmonary hemorrhage, and also the first successfully treated with bortezomib/dexamethasone.

Case report

A 52-years-old white man presented to another institution in August 2006 complaining of progressive changes in his skin that had appeared over the last 2 yr. This was associated with an unmeasured weight loss. The patient was referred to our department in December 2006. At physical examination the patient was found to have generalized cutis laxa. The patient was also found to have a highly sensitive skin with a positive guaiac and AINS test. The patient was first diagnosed with IgG-lambda monoclonal gammopathy in 2003 and was treated with dexamethasone for 3 months with no improvement. The patient was then referred to our hospital for further evaluation.

The patient was admitted to our hospital in March 2007 for a peripheral blood autologous stem cell transplant. The patient was treated with granulocyte colony-stimulating factor (G-CSF) for 5 days. A severe pulmonary hemorrhage developed during stem cells mobilization with G-CSF. The patient subsequently achieved a hematological complete response with bortezomib and dexamethasone therapy. Finally, the complete hematological response with the disappearance of the toxic M-protein allows the possibility of a long-term benefit with a kidney transplant followed by an autologous bone marrow transplant.

Abstract

The case of a 52-years-old man with generalized acquired cutis laxa associated with IgG-lambda monoclonal gammopathy and nephrotic syndrome with renal failure (due to fibrillar glomerulopathy resulting from IgG deposition) is reported. A peripheral blood autologous stem cell transplant was planned, but the procedure was complicated by severe pulmonary hemorrhage during stem cells mobilization with granulocyte colony-stimulating factor (G-CSF). Treatment with bortezomib and dexamethasone was subsequently started and a complete hematological response was achieved. Finally, the complete hematological response with the disappearance of the toxic M-protein allows the possibility of a long-term benefit with a kidney transplant followed by an autologous bone marrow transplant.

Key words generalized cutis laxa; monoclonal gammopathy; autologous transplant; pulmonary hemorrhage; renal failure; bortezomib

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medical history was unremarkable. Clinical exam only revealed high blood pressure and an inelastic and pendulous skin on his face, neck, axillae and groins. Routine laboratory work-out demonstrated a creatinine of 1.2 mg/dL and a serum M spike of 2.3 g/L in the gamma region. A skin biopsy had been performed and was considered to be consistent with morphea. The patient was treated with amlodipine for his high blood pressure.

He was first seen at our institution 1 yr later, in June 2007. The mentioned skin changes of generalized CL that gave a premature ageing appearance (Fig. 1), as well as discrete bilateral maleolar edemas was seen. A mild normocytic and normochromic anemia of 110 g/L was noted. However, his creatinine value had risen up to 2.7 mg/dL, with a 24-h urine protein excretion of 2.7 g showing a glomerular pattern. At this time, his serum M spike was of 4.4 g/L. Serum and urine immunofixation revealed an IgG-lambda monoclonal protein. A bone marrow aspirate disclosed 5% bone marrow plasma cells consistent with monoclonal gammopathy of uncertain significance. A second skin biopsy (Fig. 2) showed normal appearing dermis and epidermis specific with no inflammatory infiltrates on hematoxylin and eosin routine stains. Using orcein stain for elastic fibers there was a marked reduction of the number of elastic fibers throughout the dermis, with absent elastic fibers in some areas (Fig. 2). Direct immunofluorescence studies revealed deposition of IgG along the basement membrane zone of the dermoepidermal junction, the periadnexial and perivascular areas, and in some remaining elastic fibers in the dermis (Fig. 2). A renal biopsy showed a fibrillar glomerulonephritis (GN), with negative Congo red staining (Fig. 3). Electronic microscopy showed fibrils ranging from 10 to 15 nm. Although fibrils in fibrillary GN are reported to be thicker (10–30 nm), and amyloid fibrils are 8–12 nm thick, the distinction between these two entities cannot be made on fibril diameter alone. In fact, in one series, average fibril diameter in fibrillary GN was 14 nm (range 10.4–18.4) (10). Negative Congo Red and amyloid P-component, as well as the typical morphologic and immunohistochemistry findings were the diagnostic clues in this case.

Electrocardiogram, pulmonary functional tests, abdominal ecography and CT body scan were normal. Echocardiography only showed a mild mitral regurgitation, with normal interventricular septum and normal global motility. He was diagnosed with IgG-lambda monoclonal gammopathy associated with generalized...
adquired CL and fibrillar glomerulopathy with nephrotic syndrome and severe renal failure, both presumably secondary to IgG immunoglobulin deposition. The patient was otherwise in good general condition and so an autologous peripheral blood stem cell transplant was planned.

On the third day of stem cell mobilization with G-CSF, the patient complained of sudden dyspnea with hemoptysis that rapidly evolved into acute respiratory failure. Chest x-ray examination and a thorax CT scan showed extensive bilateral pulmonary infiltrates. All these findings, associated with a significant decrease in the hemoglobin levels and increased LDH levels at 1088 UI/L, were consistent with alveolar hemorrhage. The creatinine reached 10 mg/dL and hemodialysis was initiated. The patient improved with non-invasive mechanical ventilation, as well as treatment with high dose steroids, broad spectrum antibiotics and packed red cells transfusion support. He was finally discharged from the hospital and due to the impossibility of stem cell mobilization and the good clinical status after recovering from his pulmonary hemorrhage, he was started on a therapeutic program with i.v. bortezomib 1.3 mg/m² on days 1, 4, 8 and 11, and oral dexamethasone on days 1–4 and 9–12 at 3-wk interval. The patient has so far received 6 cycles, with a complete hematological response (disappearance of the M-spike on serum and urine electrophoresis and negative immunofixation with no increase in bone marrow plasma cells). Up to now he is still on a chronic hemodialysis program. His cutaneous condition of CL has not progressed and surgical correction of redundant skin folds is planned in the near future.

Discussion

Acquired CL is a rare condition that has been associated with monoclonal gammopathies very infrequently. Only seven cases of generalized CL associated with myeloma and four cases in the context of other plasma cell dyscrasias have been previously reported (11). Lambda light chains have been the most frequently involved, although kappa light chains have also been reported (12). Light chains, and even heavy IgG monoclonal proteins have been associated with elastolysis of the skin and glomerular alterations (2, 9).

Involvement of multiple organs by generalized elastolysis, including the gastrointestinal and genitourinary tracts, lung and cardiovascular systems, have also been reported (2). Pulmonary involvement, usually with features of emphysema, has been related to elastic fibers breakdown and loss of tissue support (13). Some authors have suggested that acquired CL could be related to an underlying genetic susceptibility associated to chronic inflammation (14). Patients with acquired CL can also develop pulmonary complications such as pneumothorax, mediastinal emphysema and pneumonia. Pulmonary involvement may also lead to secondary heart failure. To our knowledge, the occurrence of pulmonary hemorrhage in patients with CL has not been previously recognized.

A differential diagnosis in this case should include gelsolin amyloidosis, a hereditary form of amyloidosis. The main clinical manifestations are cutis laxa, corneal lattice dystrophy and cranial polyneuropathy (15). The clinical cutaneous picture is similar, probably due to direct toxic effect or an altered elastic fibrillogenesis (16). Our patient did not have any neurological alteration and, mainly, the serum M-spike and skin immunostaining revealed the presence of an IgG component. Moreover, the skin biopsy in gelsolin amyloidosis shows congophilic amyloid at the basement membranes and eccrine sweat, sebaceous glands and hairy follicles with fragmented elastic fibers (16). Renal involvement is infrequent, mainly as minor intermittent proteinuria, although nephrotic syndrome has been also described (17). High-dose therapy followed by stem cell rescue has been shown to be effective in a multiple myeloma (18,
and in other plasma cell dyscrasias. Thus, previous experiences in monoclonal gammopathies with systemic involvement and post transplant significant improvement include POEMS syndrome (20), scleromyxedema, (21, 22) and primary systemic amyloidosis (23). On the basis of this evidence, high-dose therapy followed by peripheral blood stem cell rescue was planned in our patient with the hope of improving the skin and kidney involvement by decreasing the toxic IgG M-protein. The development of an acute respiratory failure triggered by stem cell mobilization with G-CSF was completely unexpected. In vitro studies and occasional previous reports showed that the use of G-CSF can result in pulmonary toxicity, ranging from exacerbation of previous lung disease to acute lung injury, including severe pulmonary hemorrhage. Such events have been reported in patients with previously unrecognized respiratory tract involvement by amyloidosis, bleomycin lung toxicity and even in healthy donors (24–26). Granulocyte colony-stimulating factor-induced pulmonary toxicity may result from migration of neutrophils to vascular spaces, adhesion of neutrophils to previously injured endothelial cells, and/or potentiation of proinflammatory cytokines (27). It is likely that the involvement of perivascular support in the lung, similar to skin elastolysis, was the main factor contributing to the alveolar hemorrhage in our patient.

Using the same rationale as in other plasma cells dyscrasias, the patient was given treatment with bortezomib and dexamethasone. This combination has been shown to be highly effective in patients with multiple myeloma and with primary systemic amyloidosis (23, 28, 29). In addition, it can be safely administered at the usual dosing in patients with renal failure. In a series of 24 patients with dialysis dependent myeloma, the overall response rate was 75% and with no increased toxicity (30). Interestingly, Ludwig et al. have recently reported the reversal of acute paraprotein-induced renal failure with bortezomib-based therapy in five of eight patients with multiple myeloma (31). These authors suggested that bortezomib may accelerate the kidney response, not only through a rapid decrease in the M-protein concentration, but also through its NF-κB inhibitory effect, directly reducing the inflammation in myeloma kidney (32). With this background, treatment with bortezomib and dexamethasone was initiated in our patient. After six cycles of such therapy a stringent complete hematological response was achieved. As the M-protein component has disappeared, a kidney transplant followed of an autologous bone marrow transplantation in order to intensify the hematological response has been planned.

To conclude, CL syndrome related to monoclonal gammopathy is a well recognized but extremely infrequent disease. The possible involvement of other organs such of kidney or lung should be considered before any treatment is started. Although there is no previous experience in the treatment of this condition, the use of therapeutic strategies against the plasma cell clone seems most appropriate. However, physicians should be aware of the possibility of pulmonary complications with G-CSF mobilization if a peripheral blood autologous stem cell transplant is planned. The dramatic hematological response with the disappearance of the M-protein allows the possibility of a kidney transplant with no risk of immediate damage by the nephrotoxic IgG M-protein as well a subsequent safer autologous bone marrow transplant to intensify the hematological response, this increasing the likelihood of a better long-term outcome.

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References


