Abstract We report about a 58-year-old female with coexisting type-I Gaucher’s disease (GD) and multiple myeloma (MM). The diagnosis of GD was made in early childhood by means of bone marrow biopsy and was recently confirmed by analysis of the patient’s genomic DNA for the underlying glucocerebrosidase mutations and the identification of the 1226G/1448C genotype. At the age of 24 years, the patient developed massive splenomegaly. Therefore, a splenectomy was performed. No further therapy was necessary for the next 34 years until 1999 when progressive anemia and thrombocytopenia occurred. Additional laboratory analysis revealed high serum protein and immunoglobulin (Ig) G levels and evidence of monoclonal gammopathy and lambda light-chain proteinuria, indicating plasma cell dyscrasia. This diagnosis was confirmed by the detection of osteolytic lesions in skeletal X-rays and a bone marrow biopsy showing an extensive infiltration with Gaucher cells and an increase of plasma cells, which expressed lambda light chains. When examined by means of electron microscopy, typical Gaucher cells, i.e., histiocytes containing tubular-structured cytoplasmatic material and spots of plasma cells with an increase of the endoplasmic reticulum, were found. GD associated with acquired MM has been described 13 times in the literature from 1968 to 1997. Only three of the patients were suffering from IgG myeloma. This distribution of the monoclonal component is in contrast to that of patients suffering from MM alone.

Key words Gaucher disease • Plasmacytoma • Monoclonal gammopathy

Introduction

Gaucher’s disease (GD) is the most common lysosomal storage disease [1]. The disease results from a genetic deficiency of the lysosomal enzyme, glucocerebrosidase. To date, approximately 110 different mutations are known to occur in the glucocerebrosidase gene [2]. The defect of the enzyme leads to the accumulation of glucocerebrosides in macrophages. GD is separated into three main types depending on the presence and progression of neurological symptoms. Type-I GD, the most common form, is estimated to afflict more than 20,000 patients in the world’s population. The clinical symptoms are widely spread and caused by lipid-laden macrophages in the liver, spleen, and bone marrow. The patients usually suffer from progressive pancytopenia caused by hypersplenism [3]. Chronic bone pain is common. Multiple myeloma (MM), a B-cell neoplasia, accounts for about 10% of all hematologic malignancies [4]. Myeloma patients commonly suffer from weakness mostly due to anemia and bone pain caused by marrow infiltration and osteolytic bone lesions. The laboratory data usually show paraproteinemia. Coincidence of monoclonal gammopathy and GD has been reported often [5, 6]. To the best of our knowledge, the coincidence of GD and immunoglobulin (Ig) G plasmacytoma has been described only three times. We describe an additional patient and present a short review of the literature.

Case report

A 58-year-old woman was admitted to the University Hospital of Berlin with progressive anemia, thrombocytopenia, and bone pain of the small joints. In her medical history, the diagnosis of GD had been made in childhood. At the age of 24 years, massive
splenomegaly developed and a splenectomy was performed. Until the age of 58 years, no further therapy was necessary. The physical examination showed pale skin and sclera, a healed splenectomy scar, and varicosity of both legs. The liver was enlarged to 18 cm. Laboratory analysis revealed normochromic anemia with normal indices [hemoglobin (Hb) 8.8 g/dl, erythrocytes 2.7 x 10^12/l, hematocrit (Ht) 0.25%, reticulocytosis (80%), slight thrombocytopenia (118 x 10^9/l), and slight leukocytosis (12.2 x 10^9/l) with a normal differential blood smear. Increased levels of uric acid (7.6 mg/dl), total protein (11.35 g/dl), parathyroid hormone (113 ng/l), total alkaline phosphatase (266 U/l, bone isoenzyme 109 U/l), angiogenin-converting enzyme (95 U/l), gamma glutamyl transferase (36 U/l), ferritin (2523 μg/l), and viscosity (1.82 mPas) were found. Protein electrophoresis showed an IgG lambda monoclonal component with normal levels of the other fractions. IgG levels (63 g/l) were markedly elevated, while the levels of IgA (0.57 g/l) and IgM (0.27 g/l) were decreased. Proteinuria (1023 mg/24h) and Bence-Jones proteins were found. 1.25-Dihydroxy-vitamin D was reduced to 38.8 pmol/l. Mutation analysis revealed the 1226G/1448C genotype. Sonography confirmed hepatomegaly with 20 cm and cholelithiasis.

Radiological findings showed general osteoporosis, osteolytic lesions in the X-ray of the skull and the 12th thoracic vertebra, and osteosclerosis of the pelvis and the thigh. A magnetic resonance image (MRI) of the spine revealed a focal lesion of the 11th thoracic vertebra. A bone marrow aspirate and biopsy showed numerous Gaucher cells and an increased number of plasma cells arranged in clusters (Fig.1). The exact quantification of plasma cells in the biopsy sample was not possible because of the presence of Gaucher cells. The normal hematopoiesis was reduced. Immunohistochemical staining revealed a restriction of lambda light chains in the plasma cells. Electron microscopy identified Gaucher cells, i.e., histiocytes containing tubular structured cytoplasmic material and patches of plasma cells with an increase in the endoplasmic reticulum (Fig.2). The diagnosis of plasmacytoma was made using the criteria by Salmon and Durie (stage III). Because of light-chain proteinuria, anemia, and hyperviscosity, chemotherapy was indicated. Medication with oral bisphosphonates and a vitamin D substitution was started. After two courses of conventional chemotherapy with melphalan and prednisone (high-dose therapy was denied by the patient), a marked reduction of the IgG and protein levels in serum and urine was seen. At the same time, the Ht and the Hb count was increased (Table 1). After four courses of melphalan/prednisone, paraprotein levels increased again such that the therapy had to be changed to a regimen containing vincristine, adriamycin, and dexamethasone (VAD).

Cytokine levels were not available at the initiation of chemotherapy. C-reactive protein was within the normal range and remained normal during therapy. At the time of progression, plasma levels of tumor necrosis factor (TNF)-alpha and interleukin (IL)-8 were elevated to 21 pg/ml and 10.9 pg/ml, respectively, whereas IL-6 levels were normal. During VAD therapy, TNF-alpha and IL-8 levels returned to normal levels.

**Discussion**

Patients with GD frequently have diffuse hyper gammaglobulinemia, oligoclonal gammopathy, or monoclonal gammopathy of unknown significance [7]. Furthermore, the coincidence of GD with myeloproliferative disorders has been reported [8]. The coexistence of myeloma and GD has been published for 13 patients [9–20]. Seven of these patients were suffering from IgA myeloma. Three patients with non-secretory myeloma and three patients with IgG myeloma have been described. This distribution is in contrast to that of patients suffering from MM alone: the incidence amounts to 52% for IgG MM and 25% for IgA MM [21]. Similarly, M-component analysis in a Swedish population revealed 61% for IgG MM, 27% for IgA MM, and 8% for IgM MM [22]. In certain susceptible mice strains, the implantation of silicon polymers or the transfection with oncogene-containing retroviruses causes the formation of a localized inflammatory response that leads to the development of IgA plasmacytomas [23, 24]. The risk of developing malignant diseases, especially hematologic malignancies in GD patients, appears to be higher in patients suffering from GD [10]. Chronic stimulation of the immune system may be one explanation [18].

In Gaucher patients, the plasma or serum levels of IL-6 are known to be elevated [20, 25]. The raised levels may become important for IL-6-dependent plasmacytomas. Prior to therapy, IL-6 levels were not availa-