Multiple Life-Threatening Fainting Episodes: Fatal Systemic Mastocytosis

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Mastocytosis is a rare disorder characterized by overproliferation and accumulation of tissue mast cells [1]. Although the disease process often affects the skin, as in urticaria pigmentosa [2], many other organ systems may also be involved [1,2]. The clinical spectrum of the disease varies according to the involved organs and degree of mediator release. Most patients with systemic mast cell disease have indolent slowly progressing disease [1,2]. The hematologic disorders that may develop in a minority of patients have a crucial affect on the prognosis. We describe a 51 year old patient with an apparently benign disease, who suffered for three decades from recurrent fainting episodes with an eventual fatal outcome. The unusual course of his disease and the therapeutic possibilities are discussed.

Patient Description

A 23 year old healthy farmer started complaining of recurrent episodes of weakness and syncope that occurred once or twice a year. The syncope attacks lasted a few seconds and he spontaneously regained consciousness. Some of the events occurred during a febrile illness.

Physical examination including recumbent and upright blood pressure revealed no abnormal findings. Work-up, consisting of peripheral blood count, blood chemistry, blood cortisol, ACTH test, blood gases, electroencephalogram, Holter monitoring for 24 hours and urine collection for catecholamines, was perfectly normal.

Ten years later, at the age of 33, the patient noticed an increase in the frequency of the fainting episodes, up to once every 2–3 months. At that time he also experienced a prolonged loss of consciousness during an intravenous pyelography. At age 36, numerous pigmented maculopapular skin lesions sized 2–4 mm appeared on his trunk. Skin biopsy was consistent with urticaria pigmentosa. A diagnosis of SMCD was suspected and he began taking cimetidine, sodium chromoglycate and ketotifen in large doses (3–5 mg/day). Later on, different antihistamines, including loratidine and terfenadine, were added.

During the next 10 years, despite constant medical treatment, the fainting episodes did not cease. At the age of 46 he underwent a bone marrow biopsy and a definite diagnosis of systemic mastocytosis was established. Repeated blood count, liver function tests and blood chemistry were still normal. His bone scan showed no signs of osteoporosis.

One year later, during a febrile illness, he felt weak and within half an hour developed profound shock. He was resuscitated, admitted to the intensive care unit, hospitalized for 10 days, recovered completely, and upon discharge was equipped with an epinephrine auto-injector. Similar episodes of shock during febrile illness recurred, about three times a year. Resuscitation was required in all episodes, but he nevertheless made a complete recovery.

At the age of 51, while febrile, he abruptly developed cardiorespiratory collapse, but this time multiple organ failure developed and he died 2 days later. The main autopsy findings included numerous para-trabecular mast cell nodules in the bone marrow and enlarged spleen and retroperitoneal lymph nodes infiltrated with mast cells. Acute respiratory distress syndrome as well as acute bronchopneumonia was found in the lungs.

SMSD = systemic mast cell disease

Comment

Mastocytosis is a disease with a large clinical spectrum that varies according to the affected organs, the extent of mast cell proliferation, mediator release and accompanying hematologic disorders. A consensus conference on mastocytosis proposed a classification scheme [1,2] and integrated the clinical presentation and prognostic factors, defining four categories. Category I – indolent mastocytosis – has favorable prognostic features. Its symptoms include: syncope, cutaneous lesions, ulcer disease, malabsorption, bone marrow mast cell aggregates, skeletal disease, hepatosplenomegaly and lymphadenopathy. Categories II to IV define the less favorable prognostic forms and include mastocytosis with hematologic disorder (myeloproliferative or myelodysplastic), lymphadenopathic mastocytosis with eosinophilia and mastocytic leukemia.

We describe a young male patient who suffered recurrent fainting episodes for 13 years before the appearance of urticaria pigmentosa, which established the diagnosis of SMCD. The signs and symptoms of anaphylaxis may be isolated to one organ system or it may involve several. Cardiovascular collapse with shock can occur immediately without any cutaneous or respiratory symptoms [3]. Anaphylaxis was previously described as the presenting manifestation of systemic mastocytosis [4], and the majority of these patients, like the one presented here, lacked any cutaneous lesions of mastocytosis. Thus, after ruling out other possible etiologies in our patient we assume that SMCD was the only possible explanation for his long-standing symptoms. It was the eventual fatal outcome that was rather unique. Acute exacerbations of SMCD can be triggered by

fever and pharmacologic agents (contrast media), as well as by other stimuli such as external heat, exertion and emotional upset. Although the evidence for general involvement of the disease was provided by the bone marrow biopsy, its full extent could be appreciated only after the post-mortem exam. Massive mast cell infiltration as observed in the autopsy can explain the severity of the anaphylactic episodes. According to the accepted classification, our patient had the more favorable form of SMCD – category I. Although it never progressed to the less favorable category with hematologic involvement, this "benign" form of the disease resulted eventually in the patient's death. Thus, this classification with its presumed prognostic characteristics cannot always be applied in predicting the clinical outcome of a unique case, as represented by our patient.

Prompt epinephrine administration is the treatment of choice in anaphylactic reaction. Preventing these episodes as well as other symptoms of SMCD by regular usage of H1 and H2 receptor antagonists and mast cell-stabilizing agents has been recommended [2]. H1 and H2 antihistamines block the effect of histamine on peripheral organs, whereas mast cell stabilizers such as sodium cromoglycate and ketotifen prevent mast cell degranulation. These two groups of medications, which constitute the cornerstone of therapy, were given to our patient, as was EpiPen autoinjector. PUVA (psoralens with long-wave ultraviolet irradiation) have potential side effects and are recommended only for patients with massive cutaneous involvement without the involvement of any other organ [2]. Corticosteroids may exacerbate the bone disease, and for this reason should be reserved for patients with severe malabsorption [2]. Reports on the use of alpha-interferon show contradictory results [1], whereas the cumulative experience with cyclosporin has been meager, and chemotherapy is generally indicated only for patients with category II disease [2]. Bone marrow transplantation has been tried in two cases of mastocytosis associated with hematologic involvement. Although inducing remission in the myelodysplastic syndrome in one case, this mode of therapy failed to induce a similar remission in the symptoms of mastocytosis [5].

Our patient was treated with H1 and H2 blockers as well as with sodium cromoglycate and high dose ketotifen. Nevertheless, this treatment was not effective in preventing the anaphylactic episodes that became more severe and life-threatening. All other alternative treatments were considered but eventually denied because of their potential side effects and the extremely limited experience with these modalities.

The presented case describes a patient with an apparent indolent mastocytosis whose only symptom, albeit rather serious, was recurrent anaphylactic episodes over three decades. He had urticaria pigmentosa which, together with normal liver function tests, normal bone scan and no evidence of cytopenia, favored a good long-term prognosis. However, despite the good prognostic category and the comprehensive known medical treatment he was receiving, the "benign" indolent mastocytosis ended in a fatal outcome.

We conclude that SMCD must be considered in the differential diagnosis of recurrent unexplained syncope. In specific patients with category I mastocytosis associated with recurrent life-threatening anaphylactic episodes, the conventional treatment may not suffice. In view of the lack of therapeutic experience in such cases, a more aggressive approach, including the aforementioned modalities, should be considered.

References

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