

Mastocytosis, Melanoma And Sarcoidosis

M Lee-Wong, M Laufer, M Karagic

Citation

M Lee-Wong, M Laufer, M Karagic. *Mastocytosis, Melanoma And Sarcoidosis*. The Internet Journal of Asthma, Allergy and Immunology. 2008 Volume 7 Number 1.

Abstract

This report describes a 30-year-old man with a history of malignant melanoma who developed various signs, symptoms and laboratory findings which were consistent with systemic mastocytosis. The patient also developed night sweats, weight loss and dyspnea, along with bilateral hilar lymphadenopathy and diffuse pulmonary infiltrates. A transbronchial biopsy revealed non-necrotizing granulomas that were diagnosed as sarcoidosis. We believe this is the first report of melanoma and mastocytosis in the same patient, suggesting a possible genetic link between the two diseases. The pulmonary manifestations were ultimately found to be due to sarcoidosis.

INTRODUCTION

Mastocytosis is a rare condition of mast cell hyperplasia that can present as a variety of clinical syndromes^[1]. Signs and symptoms are due to mast cell mediator release as well as infiltration of organs by mast cells. Manifestations may be constitutional (fatigue, fever, malaise, weight loss), neurologic (cognitive disorganization, headaches), cardiopulmonary (chest pain, dizziness, dyspnea, palpitations, syncope), dermatological (bullae, flushing, purities, urticaria), skeletal (bone pain), and gastrointestinal (abdominal cramps, diarrhea, epigastric pain, nausea, vomiting)^[1].

Mastocytosis is classified in four groups, labeled types I, II, III and IV^[2]. Type I, indolent mastocytosis, is further subdivided into type Ia (indolent mastocytosis without systemic disease) and type Ib (indolent mastocytosis with systemic disease). Type Ia usually implies presence of cutaneous lesions, while type Ib displays evidence of mast cell infiltration of bone marrow, liver, spleen, lymph nodes, gastrointestinal tract or lungs. Mast cell mediators also contribute to such pathology as malabsorption, skeletal disease and hemodynamic instability. Patients with type I have a very good long-term prognosis^[1].

Type II is mastocytosis associated with a myeloproliferative or myelodysplastic disease. These patients may have skin manifestations but will usually have systemic symptoms of mastocytosis. The prognosis is normally dependant on the associated hematologic disorder. Type III,

lymphadenopathic mastocytosis with eosinophilia, is more rare and aggressive with a very poor prognosis. Bone marrow involvement quickly spreads to lymph nodes, as well as other organs including the gastrointestinal tract, liver, spleen, kidneys, lungs, bones and soft tissues. Mast cell leukemia constitutes type IV and also includes diffuse systemic involvement with or without cutaneous disease. Unlike type II, there is not an associated myeloproliferative or myelodysplastic disorder. The prognosis of type IV is the poorest, with an expected survival of less than 1 year^[1].

Pulmonary manifestation of mastocytosis are uncommon, although there have been several case reports. Schmidt et al reported a 54-year-old man with mastocytosis and dyspnea. This patient's lungs demonstrated a diffuse fine reticular pattern on chest radiography. Computed tomography scan revealed mediastinal lymphadenopathy as well as nodular and cystic densities in the lung interstitium, which were found to be mast cell granulomas on transbronchial biopsy^[3]. Avila et al reported a 21-year-old woman with systemic mastocytosis who also had multiple pulmonary nodules on computed tomography scans; fine needle aspiration revealed infiltration with mast cells^[4].

The etiology of mastocytosis is incompletely understood. However, there is one pathologic mechanism that is well established¹. On their cell surface, mast cells express CD117 (KIT), a tyrosine kinase encoded by the proto-oncogene c-kit located on chromosome 4q12. A point mutation in codon 816 of c-kit has been discovered in patients with mastocytosis^[5]. This mutation leads to constitutive

activation of CD117_[67], which results in continued cell division and failure of inhibition of apoptosis, allowing uncontrolled proliferation of mast cells^[8].

CD117 is normally expressed by a number of cell types in addition to mast cells, including melanocytes. In one study, CD117 expression was found in 90% of malignant melanomas^[9]. The identical mutation in codon 816 of c-kit has been detected in non-mast cell malignancies in hematopoietic lineages^[10], although not in melanoma. However, recent in vitro studies have established a strong link between CD117 (the c-kit protein) and the progression of melanoma^[11]. A case of a patient with preexisting systemic mastocytosis who then developed malignant melanoma has been reported^[12].

We present a case of a patient with a history of malignant melanoma who subsequently developed systemic mastocytosis. Additionally, this patient presented simultaneously with mastocytosis and sarcoidosis, highlighting the difficulties of identifying the pulmonary manifestations of mastocytosis. Finally, we found that the mast cell disease caused findings that had been previously attributed to other causes.

CASE REPORT

A 28 year-old man with a history of malignant melanoma and irritable bowel syndrome presented to his medical doctor with complaints of pruritis, puffy eyes and cognitive clouding. The patient was prescribed an H2 receptor-blocker, which controlled the patient's symptoms.

Several months later, over a period of three months, the patient lost 32 pounds and experienced daily night sweats and new dyspnea on exertion as well as continued pruritis and cognitive clouding. He had occasional abdominal cramping and diarrhea.

Pulmonary function tests demonstrated mild reversible obstruction. Chest radiography was unremarkable, but a chest computed tomography (CT) scan revealed mediastinal and bilateral hilar lymphadenopathy, and ground glass opacities that were diffuse in the upper lung fields with patchy, discrete round areas in the lower lung fields. Transbronchial biopsy showed non-necrotizing granulomas with absence of staining for CD117. The angiotensin converting enzyme level was normal, and a chemistry panel and hemogram were normal except for a mild thrombocytopenia. The patient was diagnosed with sarcoidosis and given prednisone.

Over the next 6 months, serial CT scans showed improvement in the lymphadenopathy and infiltrates, although reticular-nodular densities were noted where the ground glass opacities had been. Fungal and HIV antibody testing were negative.

Only two weeks later, the patient fell while skiing and was found to have multiple pelvic fractures (superior and inferior pubic rami and left sacral ala). The platelet count on was 36,000. Bone densitometry scan revealed osteopenia.

A bone marrow biopsy was performed, which showed: aggregates of mast cells, which on immunohistochemical evaluation almost exclusively express CD117 and CD68. There was no evidence of a myelodysplastic or myeloproliferative disorder.

The patient still had complaints of cognitive clouding, headaches, fatigue, dyspnea, mild abdominal cramping and pruritis. On examination, he had numerous 0.5-1.0 cm round red and brown macules and papules covering his upper back and neck, and to a lesser degree on his arms. Darier's sign was not present. He was started on anti-histaminic agents, oral cromolyn and given a subcutaneous epinephrine auto-injector for emergency use.

DISCUSSION

We report a case of systemic mastocytosis associated with malignant melanoma. When the last such report was published in 1991, the authors believed that the coexisting pathologies were more than coincidental for two reasons. The patient had no risk factors for melanoma and there had been papers published in the 1970's that established a histiogenic relationship between mast cells and melanocytes^[12].

We now know of a much stronger, genetic, potential link between the diseases. We can hypothesize that the patient has a mutation in c-kit. The defective KIT protein (CD117) may be responsible for the uncontrolled mast cell and melanocyte proliferation. Other genetic explanations would include a defect in Stem Cell Factor (SCF), the ligand that activates KIT. Additionally, there could be a problem with a specific tumor suppressor gene.

Retrospectively, we are now sure that the patient's initial presentation to his PMD with pruritis, periorbital edema and cognitive clouding was due to mastocytosis. This is consistent with his response to H2 receptor-blockers, as these symptoms are secondary to release of mast cell

mediators. However, the etiology of the second presentation is less obvious. The dyspnea, weight loss and fevers, as well as the bilateral hilar lymphadenopathy and pulmonary infiltrates, are consistent with both sarcoid and pulmonary involvement of mastocytosis. The transbronchial biopsy demonstrated non-necrotizing granulomas that were not comprised of mast cells. Infectious causes of non-necrotizing granulomas were ruled out. Thus, the patient probably did develop sarcoid as well as mastocytosis. Sarcoid is relatively common in the general population and is probably just as prevalent among those with mast cell disease.

While the patient's pulmonary symptoms are not secondary to mastocytosis, his abdominal cramping and diarrhea, which had been attributed to irritable bowel syndrome, are now better explained by mast cell disease. Furthermore, his diagnosis of osteoporosis due to corticosteroid therapy was incorrect. The duration of steroid therapy had been less than one year and osteoporosis can be caused by systemic mastocytosis[1]. The clinician should be aware of mastocytosis and alert to the common presentations of this uncommon disease.

References

1. Tharp MD, Longley, BJ. Mastocytosis. *Derm Clin* 2001;19(4):679-696
2. Valent P, Horny H-P, Escribano L, Longley JB, Li CY, Schwartz LB, Morone G, Nunez R, Akin C, Sotlar K, Sperr WR, Wolff K, Brunning RD, Parwaresch RM, Austen FK, Lennert K, Matcalfe DD, Vardiman JW, Bennett JM. Diagnostic criteria and classification of mastocytosis: A consensus proposal. *Leukemia Res* 2001;25:603-605.
3. Schmidt M, Dercken C, Loke O, Reinmann S, Diedrich S, Blasis S, Heidenreich S. Pulmonary manifestation of systemic mast cell disease. *Eur Respir J* 200;15:623-625.
4. Avila NA, Worobec AS, Ling A Hijazi Y, Metcalfe, DD. Pulmonary and ovarian manifestations of systemic mastocytosis. *Am J Rotentgen* 1996;166:969-970.
5. Nagata H, Okada T, Worobec AS, Semere T, Metcalfe, DD. C-kit mutation in a population of patients with mastocytosis. *Int Arch Allergy Immunol* 1997;113(1-3):184-186.
6. Nagata H, Worobec AS, Oh CK, Chowdhury BA, Tannenbaum S, Suzuki Y, Metcalfe DD. Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. *Proc Natl Acad Sci USA* 1995;92(23):10560-10564.
7. Longley BJ, Tyrrell L, Lu Sz, Ma Ys, Langley K, Ding Tg, Duffy T, Jacobs P, Tang LH, modlin I. Somatic c-KIT activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. *Nat Genet* 1996;

Author Information

Mary Lee-Wong, MD

Department of Medicine, Division of Allergy and Immunology, Beth Israel Medical Center

Michael Laufer, MD

Department of Internal Medicine, Beth Israel Medical Center

Merhunisa Karagic, MD

Medical Student, Ross University School of Medicine