

DISCUSSION

This patient had multiple diagnoses, including lymphadenopathic mastocytosis with involvement of the spleen, liver, abdominal lymph nodes, skeleton, bone marrow, skin, and gastrointestinal tract. He was also diagnosed with acute nonlymphocytic leukemia predated by the discovery of a biclonal gammopathy.³ Oligoclonal immunoglobulins have been observed in systemic mastocytosis, but this is the first patient with systemic mastocytosis to our knowledge with a biclonal gammopathy.² Oligoclonal immunoglobulins were found to be associated with those patients who had a secondary malignancy as well as a more malignant form of mastocytosis.² Biclonal gammopathy most commonly occurs as an IgG/IgA combination, and a significant portion (16%) of these patients are diagnosed with lymphoproliferative disorders such as lymphoma and lymphocytic leukemia.⁵

As a group, patients with systemic mastocytosis have an abnormally increased incidence of hematologic disorders and malignancies including dysmyelopoietic syndromes, myeloproliferative disorders, acute leukemia, and malignant lymphoma. Patients with systemic mastocytosis and coincident hematologic disorders have a significantly decreased survival time compared with the patients with systemic mastocytosis alone.⁶

We have presented this brief communication to provide a follow up of our "Allergy Grand Rounds" presentation on a patient with lymphadenopathic mastocytosis and biclonal gammopathy.³ Mastocytosis has

been suggested to be due to an innate oncogenic aberration in a hematopoietic stem cell resulting in abnormal mast cell proliferation.² The development of leukemia could correspond to an increased proliferation of cellular forms that possess this aberration.² Perhaps, T-cell derived mast cell interleukin growth factors (IL-3, IL-4, IL-9, IL-10) are partly involved in regulating the expression of neoplasia in a subset of patients with systemic mastocytosis.³ Finally, this case integrates biclonal gammopathy with systemic mastocytosis and the likelihood of developing malignancy.

REFERENCES

1. Frieri M, Papadopoulos NM, Kaliner MA, Metcalfe DD. An abnormal prebeta-lipoprotein in patients with systemic mastocytosis. *Ann Intern Med* 1982;97:220-1.
2. Meggs W, Frieri M, Costello R, Metcalfe DD, Papadopoulos NM. Oligoclonal immunoglobulins in mastocytosis. *Ann Intern Med* 1985;103:894-5.
3. Frieri M, Linn N, Schweitzer M, Angadi C, Pardanani B. Lymphadenopathic mastocytosis with eosinophilia and biclonal gammopathy. *J ALLERGY CLIN IMMUNOL* 1991;86:126-32.
4. Frieri M, Alling DW, Metcalfe DD. Comparison of the therapeutic efficacy of cromolyn sodium with that of combined chlorpheniramine and cimetidine in systemic mastocytosis. *Am J Med* 1985;78:9-14.
5. Kyle RA, Robinson RA, Katzmman JA. The clinical aspects of biclonal gammopathies: review of 57 cases. *Am J Med* 1981;71:999-1008.
6. Travis WD, Li C, Yam LT, et al. Significance of systemic mast cell disease with associated hematologic disorders. *Cancer* 1988;62:965-72.

C1 esterase inhibitor in pregnancy

Andrea J. Cohen, MD,^a Carl Laskin, MD,^b and Susan Tarlo, MB, BS^a

Toronto, Canada

We present a case of a pregnant woman who was admitted with repeated episodes of angioedema. Serum C1 esterase inhibitor level (C1INH) was found to be low, although C4 levels were normal. The inhibitor was reassayed in the postpartum period and was found to be within normal limits. Similar labo-

ratory findings were found in 2 of 22 asymptomatic women during and after pregnancy.

CASE REPORT

A 26-year-old woman who was in excellent health until 4 years before consultation had episodic periorbital edema and itchy eyes that lasted 4 to 5 hours and recurred initially at 2-week intervals, then recurred with increasing frequency, so that after 5 months the symptoms were present daily. Nine months after onset she began working at Wrigley's Gum Factory where she was exposed to several sugars, gum resin, and aspartame, and she noted that her symptoms occurred more frequently in the morning and during the daytime at work. One time on exposure to aspartame dust

From the Asthma Center, Division of Respiriology,^a and Department of Rheumatology,^b The Toronto Hospital, Toronto.

Reprint requests: Susan Tarlo, MB, BS, Edith Cavell Wing 4-008, Toronto Western Division, The Toronto Hospital, 399 Bathurst Street, Toronto, Canada.

1/8/38827

at work she immediately suffered an acute exacerbation of symptoms. A year later perennial rhinitis symptoms developed, at times concurrent with the angioedema, and she noted nausea, vomiting, abdominal cramps, diarrhea and flushing of her skin after ingestion of foods containing aspartame, even when it was mistakenly ingested. Her symptoms were slightly more severe in the winter, with fewer symptoms during nonworking weekends.

Three years after the onset of symptoms she moved from her house and her place of work, and symptoms cleared.

At the time of our assessment she was at 14 weeks gestation with an uncomplicated pregnancy. She was a lifetime nonsmoker and denied use of alcohol or medications. No history existed of asthma or eczema. She had a dog at home but no association from history between her symptoms and this. Family history was noteworthy for a maternal history of hay fever, but she had no family history of angioedema, urticaria, or asthma.

On physical examination the blood pressure was 124/72 mm Hg, and the rest of the examination was entirely within normal limits. The clinical diagnosis was of rhinitis, angioedema, and diarrhea related to aspartame. Prick skin tests to 12 common allergen solutions (Bencard, Mississauga, Ontario) showed small positive responses to tree mix, grass, ragweed pollen (2+ each) and dust and *Dermatophagoides farinae* (1+ each). A prick test with a saturated solution of aspartame in water was negative. Serum C1INH and complement levels, C3 and C4 (with rabbit antibody binding and laser nephelometry), were measured to rule out the possibility of hereditary or acquired C1INH deficiency. C1INH was low at 0.099 gm/L on two occasions (normal lower limit 0.14 gm/L). Her C3 was 0.9 (normal range 0.5 to 1.2 gm/L), and C4 was 0.4 (normal range 0.2 to 0.5 gm/ml), both in the normal range. C1INH measured in the postpartum period returned to the normal range at 0.14 gm/L. A double-blind oral challenge with aspartame was refused by the patient, and she continues to avoid aspartame, with a presumed clinical diagnosis of aspartame sensitivity, as has been reported by others.¹

Levels of C1INH and complements C3 and C4 were then similarly assessed in 22 pregnant women with no history of angioedema. Two had low levels of C1INH (Table I). One of these patients was 38 years old and at 24 weeks gestation, with an uneventful pregnancy. The second patient has scleroderma and was in the 13th week of gestation at the time of testing. Despite low C1INH levels, C3 and C4 levels were normal. Their pregnancies were uncomplicated, without hypertension or preeclampsia. Postpartum C1INH returned to normal in both subjects.

DISCUSSION

Historically, low levels of C1INH have been related to hereditary angioedema.^{2,3} However, in three out of

TABLE I. Levels of C1INH during pregnancy and in the postpartum period

Patient	C1INH level (gm/L) (pregnancy)	C1INH (gm/L) (postpartum)
1	0.099	0.14
2	0.12	0.24
3	0.12	0.406

23 patients, including the index case, levels of C1INH were low during pregnancy and normal after delivery. C1INH levels during pregnancy have been recently assessed,⁴ and studies by Halbmayer et al.⁵ have shown mild reductions in normal pregnancy and further reductions in patients with eclampsia and preeclampsia during the third trimester of pregnancy. The antithrombin-III levels were normal in all patients, and the mechanism of the reduction in pregnancy remains to be elucidated. Our patients had low levels of C1INH in the early second trimester, and the study by Halbmayer et al.⁵ measured reduced low levels in the third trimester. Among patients who have hereditary angioedema and became pregnant, episodes of angioedema have been reported to be fewer, even during parturition, possibly because of some of the enzyme changes during pregnancy.² We conclude that even when the clinical history is indicative, the diagnosis of hereditary angioedema should be made with caution in pregnant women.

REFERENCES

1. Garriga MM, Berkebille C, Metcalfe DD. A combined single-blind, double-blind, placebo controlled study to determine the reproducibility of the hypersensitivity response to aspartame. *J ALLERGY CLIN IMMUNOL* 1991;87:821-7.
2. Sim TC, Grant JA. Hereditary angioedema: its diagnostic and management perspectives. *Am J Med* 1990;88:656-64.
3. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976;84:580-93.
4. Ogston D, Walker J, Campbell DM. C1 inactivator level in pregnancy. *Thromb Res* 1981;23:454-5.
5. Halbmayer WM, Hopmeier P, Mannhalter C, et al. C1-esterase inhibitor in uncomplicated pregnancy and mild and moderate preeclampsia. *Thromb Haemostas* 1991;2:134-8.