**Clinical Conference**

**Recurrent Syncope Due to Systemic Mastocytosis**

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**Case Presentation**

A 59-year-old white woman, B. L., had been plagued by recurrent episodes of flushing, weakness, and dizziness that at times led to frank syncope. She had been well until December, 1974, when she experienced her first attack. This episode was characterized by the sudden onset of headache and fatigue followed by severe flushing (particularly of the face and neck), weakness of the legs, a feeling of malaise, and shortly thereafter, severe dizziness. Nevertheless, she recovered spontaneously after resting in the supine position for about 30 minutes.

After the attack, she continued to experience profound fatigue and weakness for approximately 60 minutes during which time she defecated and urinated abruptly. However, she was not incontinent during or after the attack, and no seizure activity was noted with this or subsequent episodes.

From 1974 until the end of 1982 she experienced six severe attacks, all associated with marked dizziness and syncope. She experienced numerous minor spells of a similar nature, as well, but without syncope. During two of these severe episodes she also experienced severe urticaria involving mainly the face, neck, upper limbs, and trunk. Mild dyspnea was noted with some of the attacks, although frank wheezing or stridor was notably absent. Nausea was frequently present during the attacks, but vomiting occurred only once or twice.

By 1983 the frequency of attacks had increased to a rate of one to two per month. Between 1975 and 1983, three attacks were associated with loss of consciousness for 30 to 60 minutes. She was hospitalized on these occasions, twice at another institution and once at the Massachusetts General Hospital. At the time of the latter admission, the blood pressure was noted to be 80 mm Hg systolic and was associated with a slight fever of 101°F and a tachycardia of 130 bpm. However, apart from strabismus of the right eye, which had been present since birth, and a multinodular goiter, the physical examination was unremarkable, and she recovered spontaneously after about 30 minutes.

Investigations performed during these three admissions included complete blood counts, routine biochemistries, thyroid function tests, liver function tests, urinalyses, blood cultures, electroencephalograms, and lumbar punctures for cerebrospinal fluid serology and cultures. These investigations were all normal. Electrocardiograms showed nonspecific ST- and T-wave changes, while a Holter monitor, exercise stress test, and thallium scan of the myocardium did not reveal arrhythmia or myocardial ischemia. An M-mode and 2-D echocardiogram was normal. Flow-volume loops and polytomography of the larynx and trachea excluded upper airways obstruction from the goiter. An $^{131}$I uptake was normal, and a thyroid scan showed a multinodular goiter. Chest roentgenograms demonstrated left superior mediastinal fullness consistent with thyroid enlargement, but the heart and lung fields were normal. A flat plate of the abdomen, an intravenous pyelogram, and skull and cervical spine roentgenograms were normal. An arch aortogram demonstrated a shallow plaque of the left carotid bifurcation, while a brain scan with flow studies and a CT scan of the brain with contrast were normal. Similarly, an upper abdominal CT scan and abdominal ultrasound were negative. An upper gastrointestinal series revealed a normal esophagus, stomach, and duodenum. Numerous 24-hour urinary collections for determination of 5-hydroxy indolacetic acid, vanillylmandelic acid, metanephrine, norepinephrine, and epinephrine...
revealed normal values. Urinary porphobilinogen and delta-aminolevulinic acid values were unremarkable, and a plasma serotonin value was normal.

After the last hospitalization the patient was referred to the Hypertension Unit at Massachusetts General Hospital. Physical examination at that time was unremarkable. Of note was the absence of urticaria pigmentosa and dermatographism. Nevertheless, on the basis of the history and the negative investigations detailed above, a diagnosis of systemic mastocytosis was considered and an elective admission arranged for further evaluation. Relevant investigations performed during this admission included a bone marrow biopsy, an antinuclear antibody titer, and estimations of total hemolytic complement, C$_3$, C$_4$, and C$_i$ inhibitor. These evaluations were all normal. However, an abdominal skin biopsy (Figure 1) revealed mast cell hyperplasia with 12 to 18 mast cells/high power field, located mainly in a perivascular distribution. A few mast cells were also noted in the interstitium. Urinary histamine determined by mass spectrometric assay (Dr. L. J. Roberts, Vanderbilt University) was normal (< 40 μg/24 hr) in 10 of 11 24-hour specimens and considerably elevated (126 μg/24 hr) in one.

Plasma histamine as determined by radioenzymatic assay was normal before but increased markedly (Figure 2) after the intravenous administration of morphine, 10 mg. Associated with this increase in plasma histamine, the patient experienced intense lacrimation, rhinorrhea, flushing, and palpitations, and there was a slight increase in heart rate and blood pressure (Figure 2). After this initial morphine provocation test, therapy was commenced with the H$_1$ antagonist chlorpheniramine, 8 mg four times daily, and the H$_2$ antagonist cimetidine, 300 mg four times daily. The cyclo-oxygenase inhibitor aspirin was also administered, initially with a low dose and then at 600 mg four times daily. After 3 days of therapy, plasma histamine was again determined in blood samples drawn before and after morphine, 10 mg intravenously (i.v.). As shown in Figure 2, administration of morphine was again associated with a marked increase in plasma histamine, but on this occasion the patient remained asymptomatic, and there was no change in the blood pressure or heart rate.

It should be noted that morphine, 10 mg i.v., has not been shown to cause an increase in plasma histamine when administered to subjects without systemic mas-
RECURRENT SYMPTOMS DUE TO SYSTEMIC MASTOCYTOSIS/Roberts

However, the sensitivity and specificity of this provocation test have not been determined. Additionally, morphine and other drugs that cause degranulation of mast cells should be administered only with great caution to patients with systemic mastocytosis, as profound histamine release leading to hypotension may ensue. Therapy with cimetidine, chlorpheniramine, and aspirin have been continued, and the patient has experienced no further attacks for the past 4 months.

**Discussion**

This is indeed an excellent case that illustrates a number of very characteristic clinical signs, symptoms, and laboratory findings in patients with mastocytosis. This patient exemplifies an unfortunately common problem with mastocytosis patients, which is that most of these patients currently are not recognized as having the disease. Although this patient had recurrent disabling symptomatology which at times was very severe and probably life-threatening and although she had been hospitalized for evaluation on numerous occasions, 9 years had elapsed before the possibility was considered that this patient might have mastocytosis. Dr. Robert Graham and colleagues should be commended for their sagacious clinical insight in this case. This patient also typifies the remarkable amelioration of severe symptomatology, which occurs in mastocytosis patients in response to appropriate pharmacological therapy. This highlights the importance of clinical recognition of the disease.

I will attempt in this discussion to outline many of the important clinical, laboratory, and therapeutic aspects of the disease mastocytosis. I would like to preface my remarks by indicating that most of my discussion derives from the experience we have accumulated at Vanderbilt University over the past 4 years. During this time we have evaluated and treated and now follow a very large series of patients with mastocytosis. In many respects, our experience over this time has been contrary to previous reports and discussions of this disease. Probably foremost in this regard has been the teaching that almost all patients with mastocytosis (99%) have the easily recognized lesions on the skin of...
urticaria pigmentosa. By implication, mastocytosis is a disease that can be easily diagnosed by simply looking at the skin, and in the absence of urticaria pigmentosa lesions, it has been thought that a diagnosis of mastocytosis can, in essence, be excluded. However, this view appears to be totally incorrect.

Four years ago we evaluated two patients with overwhelming histological and biochemical evidence of mastocytosis and were struck by the absence of cutaneous lesions in either of these patients. This led us to question how frequently other patients with similar symptomatology compatible with mastocytosis, but who do not have urticaria pigmentosa skin lesions, are encountered in whom the diagnosis is not considered. This query, to our amazement, has continued to uncover approximately four new cases a month at Vanderbilt University Hospital over the last 4 years. All but a few of these patients live within the immediate referral area to Vanderbilt University, and only three previously undiagnosed patients have lesions typical of urticaria pigmentosa. Therefore, in sharp contrast to previous teaching, it appears that mastocytosis without urticaria pigmentosa is not an extremely uncommon disorder but, rather, a disorder that is very commonly unrecognized. Of note is the absence of cutaneous lesions in the case presented here.

A possible reason for some discrepancies that we have encountered in the clinical and laboratory features of the disease may be that previous reports have described features of the disease almost exclusively in patients with urticaria pigmentosa. Differences apart from the presence or absence of skin lesions may, therefore, exist. Another possible factor may be that with our enhanced recognition of the disease we are encountering patients over a wide spectrum of disease severity. In the past, however, because the disease was thought to be very rare, the frequency of diagnosis may have been skewed toward patients at the severe end of the disease spectrum. Because of these differences, it is probably advisable to use at present the more general terms of common and uncommon in the discussion of the various symptoms, signs, and laboratory features of the disease until more recent experience is finally analyzed in statistical detail.

I would finally like to preface my discussion by indicating that although mastocytosis, by definition, involves an abnormal proliferation of mast cells, we encounter, not infrequently, patients in whom we can obtain, at least intermittently, biochemical evidence of increased release of mast cell secretory products but in whom we cannot obtain definitive histologic evidence of increased mast cell proliferation. It may be that our current methods to detect histologically the increased mast cell proliferation are inadequate or lack sufficient sensitivity. However, it is also conceivable that these patients do not have a disease of abnormal mast cell proliferation but a disorder of abnormal mast cell activation. Therefore, until further studies can elucidate more clearly the pathophysiology of this subset of patients, we prefer at this time to describe such patients as having a disorder of abnormal mast cell activation rather than as having mastocytosis, per se. However, it is important to recognize that this subset of patients does exist because the symptomatology, as well as its severity, is similar to that of patients in whom there is obvious increased mast cell proliferation. Moreover, the response of this former group of patients to therapy is also equally favorable.

Etiology, Natural Course, and Prognosis

The etiology of mastocytosis is essentially unknown. Although mast cells in patients with mastocytosis may demonstrate some histologic abnormalities, grossly malignant changes are rarely seen. There are factors that are known to influence mast cell proliferation in culture, but whether these factors have any influence on the endogenous proliferation of mast cells in vivo is unknown. It may be simplistic to assume there is one common etiology of mastocytosis. Perhaps supporting this contention is the fact that, although mastocytosis predominantly appears sporadically, an inherited form of this disease also occurs. Perhaps genetically transmitted mastocytosis may be more common than previously recognized. The natural course of this disease is quite variable and unpredictable. However, when mastocytosis occurs during childhood, the disease will spontaneously disappear in approximately 50% of the cases before the child reaches adulthood. When the disease initially appears in adults, it rarely regresses spontaneously. The major morbidity and mortality of the disease are primarily related to the consequences of massive mast cell mediator release, which can be associated with profound vasodilatory shock and syncope, as occurred in the case presented. Recent advances in our identification of mast cell secretory products, the primary mediators of these episodes of vasodilatation, have led to effective pharmacological therapy to prevent these attacks and have, thus, greatly improved the overall prognosis of the disease.

Classification and Signs

Numerous classifications of mastocytosis have appeared in the literature. The classification most commonly referred to is that proposed by Demis. The classification presented here (see Table 1) has been modified slightly from Demis’s classification to incorporate more recent experience. Mastocytosis can appear as a localized or systemic disease. Also, as discussed previously, there appears to be a subset of patients who are clinically indistinguishable from patients with mastocytosis. Definitive evidence of abnormal mast cell proliferation cannot be obtained from this subset. Table 1 also includes various signs that may occur in patients with mastocytosis.

In the most common form of localized mastocytosis, abnormal mast cell proliferation appears limited to the skin. Mastocytomas that appear as a solitary tumor of mast cells occur almost exclusively in children and usually respond favorably to excision, without recurrence. Numerous signs of cutaneous mastocytosis may occur. As previously discussed, cutaneous involve-
TABLE 1. Classification and Signs

<table>
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<tr>
<th>Classification</th>
<th>Signs</th>
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<tr>
<td>Localized mastocytosis</td>
<td>Without visible lesions</td>
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<tr>
<td></td>
<td>Erythematous acneiform</td>
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<tr>
<td></td>
<td>papules 1–3 mm</td>
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<td></td>
<td>Urticaria pigmentosa</td>
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<td></td>
<td>Telangiectasia macularis eruptiva perstans</td>
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<td></td>
<td>Nodular lesions</td>
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<td></td>
<td>Bullous lesions</td>
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<tr>
<td></td>
<td>Dermatographism</td>
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<tr>
<td>Solitary mastocytoma</td>
<td>Hepatosplenomegaly</td>
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<tr>
<td>Systemic mastocytosis</td>
<td>Osteoporosis and/or osteosclerosis</td>
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<tr>
<td></td>
<td>Gastrointestinal mucosal nodules 1–3 mm</td>
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<td></td>
<td>Eosinophilia</td>
</tr>
<tr>
<td></td>
<td>Anemia, leukocytosis</td>
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<td></td>
<td>Mast cell leukemia</td>
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Abnormal mast cell activation without evident abnormal mast cell proliferation


dgment in the absence of visible lesions occurs much more commonly than previously recognized. We have noticed the presence of 1 to 3 mm erythematous acneiform papular lesions. These appear evanescently. Biopsy does not indicate that these lesions represent focal accumulation of mast cells but rather papular urticarial-like lesions. That these may have a common pathogenesis with the small erythematous acneiform lesions that can be seen on the skin of some patients is speculative, but attractive.

As discussed previously, urticaria pigmentosa lesions are uncommon. Urticaria of these lesions when rubbed has been termed Darier's sign. An uncommon adult form of cutaneous mastocytosis has been termed telangiectasia macularis eruptiva perstans. This is characterized by persistent telangiectatic changes in the skin, which are presumed to result from the effect of chronic cutaneous release of the mast cell vasodilator mediators. Nodular or bullous skin lesions may occur, but they usually predominate in children with mastocytosis. Almost all patients with mastocytosis, even patients without skin lesions, will demonstrate dermatographism when the skin is stroked with a blunt instrument. This can be a clinically useful sign, but frequently the whealing takes several minutes to develop and may be overlooked unless the skin is examined for several minutes after stroking.

Previous reports have indicated that signs of systemic mast cell involvement, such as bone abnormalities and hepatosplenomegaly, occur frequently. However, we have rarely observed these abnormalities in our patients. The reason for the occurrence of both osteoporosis and osteosclerosis in systemic mastocytosis remains speculative. We have noted modest eosinophilia in a small percentage of our patients. It has been speculated that eosinophilia may occur in response to the release of eosinophil chemotactic factor of anaphylaxis (ECF-A) from mast cells. Anemia and leukocytosis does occur in mastocytosis, but we have only observed these peripheral blood abnormalities in patients with extensive abnormal proliferation of mast cells in the bone marrow. Such bone marrow involvement, however, seems to be an uncommon occurrence. Mast cell leukemia has been described but appears to be extremely rare. An abnormality that is commonly found upon radiologic examination of the gastrointestinal tract is the presence of small evanescent mucosal nodules located predominantly in the jejunum. These do not appear to represent focal accumulation of mast cells but rather papular urticarial-like lesions. That these may have a common pathogenesis with the small erythematous acneiform lesions that can be seen on the skin of some patients is speculative, but attractive.

Symptoms

The symptoms of mastocytosis (Table 2) are quite protean, are generally episodic, and are a consequence of the paroxysmal release of mast cell mediators. It is important to emphasize that these symptoms can occur in a wide variety of combinations and differ markedly in their relative severity among individual patients. Rarely is a patient encountered in whom all of the listed symptoms occur. This, therefore, leads to a vast array of clinical presentations and, undoubtedly, contributes to problems and difficulties of diagnosis. Because of the diversity of clinical presentations, the disease should not be excluded by the absence of symptom(s) included in this list. Rather, the occurrence of some combination of the symptoms should serve to heighten the suspicion of the clinician as to the possibility of mastocytosis and thus should provide a basis to pursue the diagnosis with appropriate laboratory tests, etc. The patient presented here, how-

<table>
<thead>
<tr>
<th>Table 2. Symptoms of Mastocytosis</th>
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<tr>
<td>Flushing (almost always present)</td>
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<tr>
<td>Palpitations (very common)</td>
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<tr>
<td>Dyspnea without wheezing (very common)</td>
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<tr>
<td>Dizziness (very common)</td>
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<tr>
<td>Syncope (approximately one-third of cases)</td>
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<tr>
<td>Chest pain (very common)</td>
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<tr>
<td>Headaches (very common)</td>
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<tr>
<td>Pruritis (common)</td>
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<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Chronic (rare)</td>
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<tr>
<td>Intermittent (very common)</td>
</tr>
<tr>
<td>Nausea and vomiting (common)</td>
</tr>
<tr>
<td>Chronic fatigue (very common)</td>
</tr>
<tr>
<td>Paresthesias (uncommon)</td>
</tr>
<tr>
<td>Focal neurologic signs and symptoms (uncommon)</td>
</tr>
<tr>
<td>Vertigo (common)</td>
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<tr>
<td>Central nervous system dysfunction (common)</td>
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</table>
ever, experienced almost all of the symptoms listed in Table 2.

Flushing occurs in almost all patients. Eliciting this symptom, probably more than any other symptom, should raise the suspicion for mastocytosis. However, some patients do not realize they actually appear flushed because they have never observed themselves in a mirror during an attack. In patients like this, however, a history of feeling very hot during attacks can usually be obtained. We have also found that many patients place little significance on the symptom of flushing, especially when accompanied by other severe symptoms such as syncope. Thus, they may not complain of flushing unless specifically asked. Furthermore, with a sudden massive release of mast cell mediators, the blood pressure may fall so precipitously that flushing never occurs. However, frequently flushing can be observed as the attack subsides and the blood pressure rises.

Palpitations, dizziness, and dyspnea occur frequently during attacks. Interestingly, in contrast to IgE-mediated anaphylaxis, wheezing is an extremely uncommon occurrence in mastocytosis. Frank syncope occurs during attacks in approximately one-third of the cases. Chest pain during attacks is very common. Although the etiology of the chest pain is unclear, esophageal spasm is a possible explanation. We have not observed electrocardiographic evidence of ischemia in patients experiencing chest pain during attacks. In some patients, the chest pain may be excruciating and the presenting chief complaint, although in most patients the pain is only slight. Many patients complain of frequent recurrent headaches; the occurrence of frequent recurrent headaches is very common. Pruritis is also common. Chronic fatigue is extremely common. Not infrequently, as apparently was the case in the patient presented today, this fatigue can severely impair the individuals ability to work or even do normal household tasks. Even in the absence of chronic fatigue, almost all patients (as did this patient) experience extreme fatigue after an attack that can last hours or days. This can be clinically helpful to distinguish other causes of syncope such as arrhythmias, which are not characterizedly associated with prolonged severe fatigue, and prostration following return of consciousness. Paresthesias sometimes occur at the onset of attacks. Some patients also have had proxysmal focal neurologic symptoms such as weakness and numbness in an upper extremity. The pathogenesis of this is unclear. Some patients describe vertiginous episodes that may not be temporally related to their attacks of flushing. This patient apparently experienced loss of equilibrium early during the onset of an attack. Finally, many mastocytosis patients complain of emotional lability, loss of memory, and difficulty in concentration. The occurrence of these central nervous system abnormalities in mastocytosis has recently been well documented, although the pathogenesis remains unclear.

### Provoking Factors of Mast Cell Activation

Patients with mastocytosis typically experience the above symptoms paroxysmally as discrete attacks. What then suddenly evokes the non-IgE-mediated synchronous systemic activation of mast cells? Unfortunately, the answer to this question is largely unknown. There are situations, however, which many patients recognize, that will frequently precipitate an attack. The biochemical mechanisms involved are not understood. Very commonly patients will relate that physical exertion, emotional anxiety, or heat, at times, will cause an attack.

In addition to endogenous factors that can influence mast cell activation, a number of pharmacological agents are known to evoke mast cell activation and thus should be avoided in patients with mastocytosis. These potentially hazardous agents are listed in Table 3.

<table>
<thead>
<tr>
<th>Pharmacological Mast Cell Activators</th>
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<tr>
<td>Narcotic analgesics</td>
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<tr>
<td>Radiologic contrast dye</td>
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<tr>
<td>Alcohol</td>
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<tr>
<td>Muscle relaxants</td>
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<tr>
<td>Any intravenous medication (preservatives)</td>
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<tr>
<td>Nonsteroidal, anti-inflammatory drugs</td>
</tr>
<tr>
<td>Beta adrenergic receptor antagonists</td>
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<tr>
<td>Alpha adrenergic receptor agonists</td>
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<tr>
<td>Cholinergic receptor agonists</td>
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Most of these agents have been shown to evoke mast cell degranulation in vitro. In the patient described here, intravenous morphine caused flushing and histamine release. Although narcotic analgesics like morphine can cause severe attacks in some patients with mastocytosis, this response does not appear to be uniform as we have encountered patients who have received these drugs with no untoward reaction. Many of these drugs, commonly and routinely used during anesthesia and surgery, are potentially hazardous when administered to patients with mastocytosis. Mastocytosis patients can undergo surgical procedures safely if they are diagnosed preoperatively and if potentially hazardous drugs are avoided. Two of the most important pharmacological agents to recognize that can be associated with severe and potentially lethal reactions when given to mastocytosis patients are the nonsteroid anti-inflammatory drugs and beta-adrenergic receptor antagonists. Approximately 5% of patients with mastocytosis have aspirin hypersensitivity. A similar percentage of patients with chronic asthma also have aspirin hypersensitivity. For these patients the ingestion of miniscule doses of aspirin or any nonsteroidal anti-inflammatory drug can evoke severe bronchospasm. In the mastocytosis patient who demonstrates this phenomenon, ingestion of these drugs does not evoke severe bronchospasm but can cause profound cardiovascular collapse. Although the mechanisms involved in these reactions are not understood, it seems clear that these reactions are not drug-induced.
allergic reactions as any nonsteroidal anti-inflammatory drug can evoke the reaction. Thus, the triggering event is inhibition of prostaglandin biosynthesis which, in some way, leads to activation of mast cells. We have provided recent evidence that the site of inhibition of prostaglandin production that triggers mast cell activation is not within the mast cell itself. We have observed that as little as 20 mg of aspirin has evoked severe flushing and hypotension in mastocytosis patients with aspirin hypersensitivity. In such patients, the administration of a single 325 mg tablet of aspirin would very likely cause a lethal reaction. Therefore, it is extremely important to recognize that this problem exists in a subset of patients with mastocytosis.

Beta-adrenergic receptor agonists are known to inhibit mast cell degranulation in vitro. In addition, we have shown that the beta-receptor agonist epinephrine is very effective in reversing severe vasodilatory hypotension in mastocytosis at doses that are associated with only very modest direct effects on the cardiovascular system. This suggests that the mechanism by which epinephrine exerts its effect in this situation is the inhibition of mediator release as a result of mast cell beta-adrenergic receptor activation. Undoubtedly, during vasodilatory attacks in mastocytosis there is increased release of epinephrine from the adrenal medulla which may serve favorably to attenuate the severity of the attack. We have, in fact, encountered patients in whom attacks were never associated with syncope except during beta-receptor antagonist therapy. In addition, beta-receptor antagonists would also render attacks refractory to treatment with epinephrine. For these reasons, administration of beta-receptor antagonists seems clearly contraindicated in patients with mastocytosis.

Mast Cell Mediators Responsible for Symptoms
What mast cell secretory products are primarily responsible for the symptoms of mastocytosis, in particular, for the potentially life-threatening episodes of vasodilatory shock? Previously it was thought that these symptoms were attributed to the release of histamine. However, it is puzzling that antihistamine therapy did not successfully prevent recurrent episodes of vasodilatation in patients with this disease. We initially encountered two mastocytosis patients with recurrent episodes of severe flushing and hypotension in whom administration of both histamine H sub 1 and H sub 2 receptor antagonists had little appreciable effect in preventing the recurrence of these attacks, or in reversing the hypotension when the antagonists were administered intravenously during acute attacks. The question whether a mediator, in addition to histamine, was participating in these episodes of vasodilatation led to the discovery in 1980 that these patients were markedly overproducing prostaglandin D sub 2 (PGD sub 2). This finding seemed of potential significance since PGD sub 2 is a very potent vasodilator when administered to some experimental animals. The source of PGD sub 2 overproduction in these patients was the mast cell itself. Therefore, it is extremely important to recognize that this problem exists in a subset of patients with mastocytosis by our demonstration that mast cells in vitro produced essentially a single product of the cyclo-oxygenase, PGD sub 2. After subsequently developing a mass spectrometric assay for a urinary metabolite of PGD sub 2, we have shown that mast cells in vitro produced 9 alpha-hydroxy-11,15-dioxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic acid, which is used to generalize the initial finding of overproduction of PGD sub 2 in other patients with mastocytosis. Up to 150-fold increases in endogenous production of PGD sub 2 have been found to occur in patients with mastocytosis. Whereas antihistamine therapy alone has not been found successful in preventing recurrent episodes of flushing and hypotension, we have found that the recurrence of these attacks can be effectively prevented through antihistamine therapy combined with administration of drugs like aspirin that inhibit prostaglandin biosynthesis. This experience, therefore, strongly implicates PGD sub 2 as an important mast cell mediator of these vasodilatory episodes.

Keys to the Diagnosis
What are the keys to making a diagnosis of mastocytosis? It cannot be overemphasized that the diagnosis will almost never be made unless the clinician first recognizes that the symptom complex in the patient is compatible with mastocytosis and then pursues specific tests to confirm the diagnosis. This is because almost invariably, at least in the absence of urticaria pigmentosa, the routine physical examination and routine laboratory evaluation do not reveal any abnormalities.

Therefore, a major key in the diagnosis is recognition of symptoms compatible with mastocytosis. The presence of urticaria pigmentosa lesions is diagnostic but rarely found. The presence of dermatographism and small erythematous acniform lesions can be helpful in the evaluation but cannot be considered diagnostic. Histologic evidence of normal mast cell proliferation with skin and bone marrow biopsy is very helpful, but, as previously discussed, both skin and bone marrow can be normal in patients in whom increased release of mast cell mediators is documented. The finding of small mucosal nodules in the gastrointestinal tract can also be helpful in diagnosis. The most important aspect to note for diagnosis is biochemical evidence of increased release of mast cell mediators. Mast cells contain heparin. During severe attacks of flushing and hypotension, sufficient heparin can be released to prolong the partial thromboplastin time (PTT). If this occurs and the PTT can be normalized with protamine, this is very presumptive evidence that mast cell activation was associated with the episode. Demonstration of overproduction of histamine and PGD sub 2 is very important diagnostically.

At this time, unfortunately, the assay for the PGD sub 2 urinary metabolite is only established in a single laboratory, and thus is not readily available. Plasma and urinary histamine is more easily determined, but accuracy problems exist with widely used nonphysical methods for histamine measurement. We have developed an accurate mass spectrometric method for the
determination of histamine, but this method is not generally available. 40

Another problem in diagnosis of mastocytosis, in addition to analytical problems, has been that increased amounts of urinary histamine are not always excreted in patients with well-documented mastocytosis. Measurement of urinary histamine metabolite levels in these patients may be a more sensitive index of overproduction of histamine, but, again, these assays are not available. 41, 42 However, we have found that in patients with a normal urinary excretion of histamine during quiescent phases of their disease, it is usually possible to demonstrate increased urinary excretion of histamine in fractional urine collected for about 4 hours following an attack of flushing, and so forth. Therefore, short-term urine collection immediately following an attack can be extremely important in attempting to obtain evidence for increased release of histamine in patients suspected of having mastocytosis.

Treatment

Acute Vasodilatory Episode

As briefly discussed previously, we have found that doses of epinephrine that are associated with only modest direct cardiovascular effects very effectively reversed severe vasodilatory hypotension in mastocytosis. 32, 43 The primary mechanism by which epinephrine exerts its effect in this situation may be via stimulation of beta-receptors on mast cells, an effect that may inhibit further mediator release. Epinephrine can be administered either subcutaneously, intravenously, or by inhalation. Subcutaneous administration of 300 μg is usually effective in reversing hypotension, but the effect may be short-lived and hypotension may recur after several minutes. Thus, the preferred route of administration is continuous intravenous infusion. An initial subcutaneous dose can, however, serve as a temporizing measure until an intravenous catheter can be inserted. The intravenous dose of epinephrine that we have found to be effective and relatively safe is an infusion of 2 to 10 μg/min. In practice, we usually begin with a dose of 4 μg/min, which can be rapidly and conveniently prepared (1 cc 1:1000 epinephrine in 250 ml saline run at 1 ml/min). The dose can then be adjusted upward or downward depending on the response. We have maintained patients on continuous infusions of epinephrine at doses in the range of 4 μg/min for up to 24 hours without untoward effects. For outliers who have experienced severe attacks, we usually instruct them to carry either an ANA-kit (Hollister-Stier, Atlanta, Georgia) or an Epi-Pen (Center Laboratories, Port Washington, New York), which are predosed syringes of 300 μg of epinephrine for subcutaneous self-administration. However, inhalation of epinephrine via an Epi-Medihaler (Riker Laboratories, Northridge, California) is more convenient for many patients and apparently effective. Another advantage to administration through inhalation is that repeated doses can be taken until the patient reaches the emergency room if the effect of a single dose is short-lived.

Chronic Pharmacological Therapy

Chronic pharmacological therapy to prevent recurrent episodes of vasodilatation is directed at inhibiting the effects of the released histamine as well as at inhibiting the production of PGD2. To prevent the effects of histamine release, we routinely have administered the H1 receptor antagonist chlorpheniramine 4 mg (2 tablets 4 times daily) and either the H2 receptor antagonist cimetidine 300 mg (1 tablet 4 times daily) or ranitidine 150 mg (1 tablet twice daily). It is important to block both H1 and H2 receptors. As we have previously shown, there are important H2 receptors in human vasculature and to prevent the vascular effects of histamine effectively in humans requires blockade of both H1 and H2 receptors. 44 An alternative to chlorpheniramine can be doxepin (Sinequan, Roerig, New York), which was recently found 45 to have extremely potent antihistaminic effects, even at very small doses in the range of 10 to 20 mg/day. Although most patients will initially experience drowsiness from chlorpheniramine, this rarely persists after 7 to 10 days of continued administration. In our experience, the most critical aspect of therapy is inhibition of PGD2 biosynthesis. To accomplish this, we routinely use the drug aspirin. Although any nonsteroidal, anti-inflammatory drug can be used to inhibit prostaglandin production, we prefer aspirin for two reasons. Firstly, aspirin is not expensive. Secondly, and more important, aspirin therapy can be closely monitored with plasma salicylate levels, whereas the plasma level determination of other nonsteroidal, anti-inflammatory drugs is generally not available. This is an important consideration as rather marked interindividual variations in drug plasma levels have been demonstrated in individuals given identical doses of a drug such as indomethacin.46 We have found that effective control of the symptoms of mastocytosis, especially in patients with severe attacks, requires a rather high plasma salicylate level, in the range of 20 to 30 mg/dl. When the plasma level is below 20 mg/dl, attacks frequently continue to occur, although they may be less severe. The dose of aspirin usually required to achieve a plasma salicylate level between 20 to 30 mg/dl is usually in the range of 3.9 to 5.2 g/day. However, we have observed a very wide international variation in the dose of aspirin required to achieve these levels. In patients who cannot tolerate these doses of aspirin, usually because of tinnitus, other nonsteroidal, anti-inflammatory drugs such as naproxen or piroxicam should be substituted.

As discussed previously, about 5% of patients with mastocytosis have been found to have aspirin hypersensitivity. In these patients, ingestion of miniscule doses of any nonsteroidal, anti-inflammatory drug can potentially evoke life-threatening cardiovascular collapse. Therefore, initiation of aspirin therapy in mastocytosis patients must be undertaken with extreme caution. If a reliable history of frequent and recent aspirin ingestion without untoward effect can be obtained, aspirin may be given initially at single doses of 325 mg with relative safety. However, in the absence of a recent history of aspirin ingestion, initial doses admin-
istered should probably not exceed 20 mg. This dose can then be doubled at each dosing interval of 6 hours in the absence of a reaction to the previous dose until therapeutic doses are achieved. A history of recent ingestion of aspirin without untoward effect is important, as we have observed patients who could tolerate aspirin before the onset of their symptoms of mastocytosis but who reacted to aspirin after developing the disease. Such a phenomenon is understandable, given that mast cells are activated during these reactions. Epinephrine also can effectively reverse aspirin-evoked attacks of flushing and hypotension.

One obvious, important question is how should the aspirin-hypersensitive mastocytosis patient be treated? These patients are indeed therapeutically problematic. Although associated with little likelihood of success, the efficacy of antihistamine therapy alone can be assessed. Oral disodium cromoglycate has been shown to effectively control the systemic symptoms of mastocytosis in some patients, although the mechanism by which this drug exerts its effect in these patients is unclear. Not only is this drug extremely expensive, but also there is usually a delay of up to 4 to 6 weeks before an effect of the drug is realized. This delay in onset of effect can be a serious drawback in patients with frequent, potentially life-threatening episodes of flushing and hypotension. Furthermore, the percentage of patients who respond to this therapy is not well defined, but certainly not all patients experienced control of symptoms with disodium cromoglycate therapy, even with doses of approximately 400 mg/day.

The remaining therapeutic option in aspirin-hypersensitive patients is to attempt to induce tolerance to aspirin administration. In aspirin-hypersensitive asthmatics, it was recently found that if small doses of aspirin were administered repeatedly, which evoked somewhat less than life-threatening bronchospasm, after a variable number of repeated doses the patient would cease to react to further administration of aspirin or other nonsteroidal, anti-inflammatory drugs. The dosage of these agents could then be increased without untoward reaction. If, subsequently, the administration of aspirin was discontinued, there was a refractory period of about 3 to 4 days after which small doses of aspirin again evoked bronchospasm. We have also recently demonstrated that it was possible to induce tolerance to aspirin in one patient with aspirin-hypersensitive mastocytosis. After several days of repeated dosing with 10 mg aspirin, which evoked marked flushing and, on occasion, hypotension, the patient ceased to react and the dose was increased to 5.2 g/day without untoward reaction. Rather, there was substantial improvement in control of symptomatology. This procedure, however, is not without risk because it is not known how severe the reaction may be after administration of aspirin. Also, it is virtually impossible to generalize from this one patient how safe and successful desensitization would be in other patients with aspirin-hypersensitive mastocytosis. Therefore, at this time, this procedure should be considered investigational and cannot currently be recommended.

Concluding Remarks

In summary, I have attempted to briefly outline some of the important features manifested by patients who experience non-IgE-dependent paroxysmal release of mast cell mediators. Although previously it was thought that, in essence, all such patients exhibited cutaneous lesions of urticaria pigmentosa, it has now become evident to us that mastocytosis without urticaria pigmentosa is not an uncommon disorder but, rather, is a commonly unrecognized disorder. The symptomatology experienced by these patients is very protean and can masquerade and mimic a wide variety of unrelated medical disorders. Recent advances in our understanding and identification of mast cell mediators (in particular, PGD₂) which have been responsible for disabling and sometimes life-threatening symptoms have engendered, to some extent, effective control of these symptoms pharmacologically. However, much still remains unknown about the etiology, pathology, and pathophysiology of the disease(s). Students attempting to answer the many fascinating puzzles of mastocytosis will undoubtedly have a full curriculum for some time to come.

References

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Questions and Answers

Dr. Jonathan Moss (Massachusetts Eye and Ear Infirmary): The primary problem with antihistamine therapy is that the maximal occupancy of the H1 receptor by Benadryl or conventional antihistamines is only 25%, yet most biochemical responses require 50% occupancy to produce pharmacological blockade. There are a number of new combined H1 and H3 receptor antagonists that produce approximately 80% receptor occupancy. Have you tried any of these?

Dr. Roberts: We haven't tried any of the combined H1/H3 receptor antagonists. When we treat patients with high doses of antihistamines plus aspirin they do extremely well. We might consider alternative agents if we were not successful with our current regimen.

Dr. Henry Kronenberg (Endocrine Unit, Medical Service, Massachusetts General Hospital): In a disease like this, which must be somewhat uncommon yet which displays such common symptoms, it is important to know whether other conditions can raise the histamine or the prostaglandin D2 (PGD2) levels in the urine. Are there other causes of syncope or flushing that can give falsely positive elevations of histamine or PGD2?

Dr. Roberts: The gastric carcinoid syndrome is known to be associated with the release of histamine, and it is possible to effectively abolish the flushing with the administration of H2 and H3 antagonists. Certainly, everybody with flushing should have a test done for 5-hydroxy indoleacetic acid (SHIA) level to exclude the diagnosis of carcinoid syndrome. There is a very uncommon subset of patients with medullary carcinoma of the thyroid who also have episodes of flushing and hypotension. We have studied one of these patients. During an attack, this patient had very dramatic rises of circulating metabolites of both prostaglandin D2 (PGD2) and prostaglandin F2-alpha (PGF2α). Prostaglandin F2α, however, is a potent vasoconstrictor. We have demonstrated recently in a metabolic study that the intravenous injection of PGD2 in humans resulted in a marked increase in the urinary excretion of metabolites having a PGF2α ring structure. We would, therefore, speculate that the PGF2α metabolite appearing in this patient arose from the metabolism of PGD2 released from the tumor.
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