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Increased Formation of Thromboxane *In Vivo* in Humans with Mastocytosis

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Clinical manifestations of mastocytosis are mediated, at least in part, by release of the mast cell mediators histamine and prostaglandin D_2. It has been previously reported that in addition to prostaglandin D_2, mast cells produce other eicosanoids, including thromboxane. Nonetheless, little information exists regarding the formation of other prostanoids *in vivo*. The most accurate method to examine the systemic production of eicosanoids *in vivo* is the quantitation of urinary metabolites. We previously developed a highly accurate assay employing mass spectrometry to measure a major urinary metabolite of thromboxane, 11-dehydro-thromboxane B_2, in humans. We utilized this assay to quantitate thromboxane production in 17 patients with histologically proven mastocytosis. We report that thromboxane formation was significantly increased (>2 SD above the mean) in at least one urine sample from 65% of patients studied. Of these, 91% of patients with documented systemic involvement had elevated thromboxane generation. In addition, endogenous formation of thromboxane was highly correlated with the urinary excretion of the major urinary metabolite of prostaglandin D_2 ($r = 0.98$) and N^{τ}-methylhistamine ($r = 0.91$), suggesting that the cellular source of increased thromboxane *in vivo* could be the mastocyte. Enhanced thromboxane formation in patients with this disorder is unlikely to be of platelet origin as other markers of platelet activation, platelet factor 4 and β-thromboglobulin, were not increased in three patients with marked overproduction of thromboxane. Furthermore, the recovery of 11-dehydro-thromboxane B_2 excretion in two patients after the administration of aspirin occurred significantly more rapidly than the recovery of platelet thromboxane generation. These studies, therefore, report that thromboxane production is significantly increased in the majority of patients with mastocytosis that we examined and provide the basis to elucidate the role of this eicosanoid in disorders of mast cell activation. ***Key words: histamine/prostaglandin D_2/thromboxane B_2/urticaria pigmentosa. J Invest Dermatol 113:93–97, 1999***

Mastocytosis is a chronic disorder characterized by excessive proliferation of mast cells in various organs (Roberts *et al*, 1998). It can be clinically limited to the skin (cutaneous mastocytosis) or involve multiple organs throughout the body (systemic mastocytosis). Many patients with only cutaneous disease on clinical examination, however, demonstrate increases in mast cell numbers in the bone marrow (Guzzo *et al*, 1991). Patients with systemic mastocytosis frequently experience episodes of mast cell activation, characterized by intense flushing accompanied by light headedness or syncope, gastrointestinal disturbances, and other varied symptoms (Roberts *et al*, 1998). Although these episodes of mast cell activation had been attributed to the release of increased quantities of histamine from mast cells, treatment with antihistamines was not found to prevent the episodes (Hirschowitz and Groarke, 1979; Roberts *et al*, 1980). Subsequently, it was found that large quantities of prostaglandin (PG) D_2 are released in addition to histamine during episodes of mast cell activation in patients with mastocytosis and PGD_2 has been found to be an important mediator of the humoral manifestations of the disease (Roberts and Oates, 1991).

Although PGD_2 has been reported to be overproduced during mastocyte activation, little information exists regarding formation of other eicosanoids in this disorder, particularly *in vivo*. It has been previously reported that rat peritoneal mast cells in culture produce, in addition to PGD_2, large amounts of prostacyclin (PGI_2), thromboxane (Tx) and $PGF_{2\alpha}$ (Roberts *et al*, 1979). In contrast, in the human mast cell leukemia line HMC-1, substantial amounts of PGD_2, TxB_2, PGE_2, and $PGF_{2\alpha}$ are formed but very little PGI_2 can be detected (Macchia *et al*, 1995). A single study in humans reported that plasma levels of TxB_2 are significantly increased in humans with mastocytosis whereas quantities of 6-keto-$PGF_{1\alpha}$ (the stable hydrolysis product of PGI_2) are decreased (Ouwendijk *et al*, 1983). Unfortunately, these latter findings are difficult to interpret as plasma levels of both TxB_2 and 6-keto-$PGF_{1\alpha}$ are unreliable indices of systemic Tx and PGI_2 production, respectively, owing to the fact that eicosanoids are readily generated by cellular elements during blood sampling (Catella *et al*, 1986; Patrono, 1989). Thus, whereas Tx is produced by mast cells *ex vivo*, whether Tx generation

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Abbreviations: MS, mass spectrometry; NICI, negative ion chemical ionization; Tx, thromboxane.

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is increased in patients with mastocytosis *in vivo* has not been firmly established.

The most accurate method to examine the systemic production of eicosanoids *in vivo* is the quantitation of urinary metabolites (Frolich *et al*, 1975; Catella *et al*, 1986). Previously, we developed an assay to measure a major urinary metabolite of Tx, 11-dehydro-TxB_2, utilizing gas chromatography (GC)/negative ion chemical ionization (NICI) mass spectrometry (MS) (Morrow and Minton, 1993). This method is a highly accurate tool to assess the endogenous production of Tx in humans. We have now utilized this assay to quantitate Tx production in 17 well characterized individuals with mastocytosis. We report that Tx generation is significantly increased in the majority of these patients. In addition, excretion of 11-dehydro-TxB_2 correlates closely with increased formation of the two mast cell mediators, PGD_2 and histamine.

MATERIALS AND METHODS

Materials $[^2H_4]N^\tau$-methylhistamine was obtained from Merck, Sharp, Dohme (MSD) isotopes (Montreal, Quebec, Canada). $[^2H_4]$11-dehydro-TxB_2, $[^2H_3]$2,3-dinor-6-keto-$PGF_{1\alpha}$, and $[^2H_3]TxB_2$ were purchased from Cayman Chemical (Ann Arbor MI). The major urinary metabolite of PGD_2 (PGD-M), 9α,11β-dihydroxy-15-oxo-2,3,18,19-tetranor-prost-5-ene-1,20-dioic acid, was synthesized and converted to the $[^{18}O_4]$-labeled internal standard as described (Morrow *et al*, 1991).

Measurement of 11-dehydro-TxB2, 2,3-dinor-6keto-$PGF_{1\alpha}$, PGD-M, and N^τ-methylhistamine in urine 11-dehydro-TxB_2, 2,3-dinor-6-keto-$PGF_{1\alpha}$, PGD-M, and N^τ-methylhistamine were all measured in urine by highly accurate, stable isotope GC/NICI MS assays (Morrow *et al*, 1991, 1995; Morrow and Minton, 1993; Daniel *et al*, 1994). The precision and accuracy of the assays are as follows: for 11-dehydro-TxB_2 7% and 90%; for 2,3-dinor-6-keto-$PGF_{1\alpha}$ 5% and 98%; for PGD-M 7% and 96%; and for N^τ-methylhistamine 2% and 97%. The urinary creatinine concentration was measured by the sodium picrate method with an AutoAnalyzer II (Technicon, Tarrytown, NY). The levels of N^τ-methylhistamine were expressed as pmol per μmol creatinine and levels of eicosanoid metabolites as pmol per mmol creatinine. The normal range for each substance was determined by measurements in 20 normal volunteers.

Quantitation of platelet factor 4 and β-thromboglobulin in plasma and TxB_2 in serum Levels of platelet factor 4 and β-thromboglobulin in three patients with mastocytosis were quantitated in plasma utilizing radioimmunoassays (Nichols *et al*, 1982). TxB_2 was measured in serum *ex vivo* after platelet activation by endogenous thrombin during whole blood clotting at 37°C as described employing GC/NICI MS (FitzGerald *et al*, 1983).

Clinical studies We evaluated 17 patients, 11 women and six men, who had histologically documented urticaria pigmentosa skin lesions. The clinical characteristics and urinary levels of N^τ-methylhistamine and PGD-M in these individuals have been previously reported (Morrow *et al*, 1995). The patients ranged in age from 20 to 65 y. All patients had scattered urticaria pigmentosa lesions on at least 40% of their body surface. Fifteen of the 17 individuals underwent bone marrow biopsies to assess whether systemic involvement was present. Patients were admitted to the hospital, and 24 h urine collections obtained for measurements of eicosanoids and N^τ-methylhistamine after 48 h of a standardized low histidine, low histamine diet to minimize dietary influences on levels of N^τ-methylhistamine. A total of 46 urine samples were collected. All urine samples were stored at –70°C until analyzed. None of the patients had taken nonsteroidal anti-inflammatory drugs for at least 1 wk before the study.

In two patients with mastocytosis, an additional study was performed to compare the suppression and recovery of endogenous Tx and PGD_2 generation in response to aspirin treatment. Each individual was treated with oral aspirin 160 mg twice daily for 4 d. Systemic Tx formation is maximally inhibited by this dosage of aspirin (FitzGerald *et al*, 1983, 1987). Urine and serum were collected before treatment and then daily on days 1–8 after therapy was stopped. Urine was quantitated for 11-dehydro-TxB_2 and PGD-M and TxB_2 was measured in serum.

Statistical analyses Where appropriate, data was analyzed using linear regression analysis and correlation employing Graphpad Instat Software version 1.13 (Graphpad, San Diego, CA).

Table I. Clinical and laboratory data in 17 patients with mastocytosis

Patient	Age/sex	Urticaria pigmentosa	Symptoms	Nodules in bone marrow
A	44/F	+	–	–
B	39/M	+	–	–
C	46/F	+	+ (flushing, dizziness)	–
D	43/F	+	–	–
E	22/M	+	–	Not performed
F	20/F	+	–	Not performed
G	38/F	+	–	+
H	30/M	+	–	+
I	32/M	+	–	+
J	40/M	+	+ (flushing, dizziness)	+
K	23/F	+	–	+
L	30/M	+	+ (syncope)	+
M	27/F	+	+ (syncope)	+
N	34/F	+	–	+
O	33/F	+	–	+
p	45/F	+	+ (flushing)	+
Q	65/F	+	+ (syncope)	+

RESULTS

Clinical and laboratory data in patients with mastocytosis **Table I** summarizes the clinical and laboratory findings in 17 patients examined in this study. The patients can be separated into three groups: four patients with cutaneous mastocytosis with no evidence of bone marrow involvement (patients A–D); 11 patients with evidence of both cutaneous and marrow involvement (patients G–Q); and two patients with cutaneous disease who were not evaluated for the presence of bone marrow involvement (patients E and F).

Urinary levels of 11-dehydro-TxB_2 are increased in the majority of patients with mastocytosis In 20 normal volunteers, urinary levels of 11-dehydro-TxB_2 were 118 ± 88 pmol per mmol creatinine (mean ± 2 SD). Urinary 11-dehydro-TxB_2 levels measured in 17 patients with mastocytosis are shown in **Fig 1**. The horizontal dashed line denotes the upper limits of normal (2 SD above the mean) for urinary 11-dehydro-TxB_2 levels. In only six of 17 patients (35%) (patients A–E, H) was the urinary excretion of 11-dehydro-TxB_2 normal in all urine collections. In contrast, in 10 of 17 patients (59%) (patients G, I–Q), 11-dehydro-TxB_2 were abnormally elevated in all urine collections whereas in one patient (patient F), one of two urine collections had an marginally elevated 11-dehydro-TxB_2 level. In patient Q, increases in Tx excretion were up to 48-fold above the upper limits of normal. Therefore, the majority (65%) of patients in this study had an elevated 11-dehydroTxB_2 level in at least one 24 h urine collection. Interestingly, of the individuals with increased Tx excretion, all but one (91%) had evidence of systemic involvement whereas no patients without evidence of systemic disease had elevated levels of 11-dehydroTxB_2. In comparison, we have previously reported that 94% of these patients had increased excretion of PGD-M in at least one 24 h urine collection and 71% had at least one urine sample with elevated N^τ-methylhistamine (Morrow *et al*, 1995).

Correlation between the excretion of 11-dehydro-TxB_2, PGD-M, and N^τ-methylhistamine in patients with mastocytosis **Figure 2** compares the levels of 11-dehydro-TxB_2 and PGD-M for the urine samples shown in **Fig 1**. The vertical and horizontal dashed lines represent the upper limits of normal values for 11-dehydro-TxB_2 and PGD-M, respectively. As is evident, increases in urinary excretion of 11-dehydro-TxB_2 are highly associated with and proportional to increases in levels of PGD-M in the same samples. The correlation coefficient (r) for the relationship is 0.98 and $r^2 = 0.95$ ($p < 0.0001$).

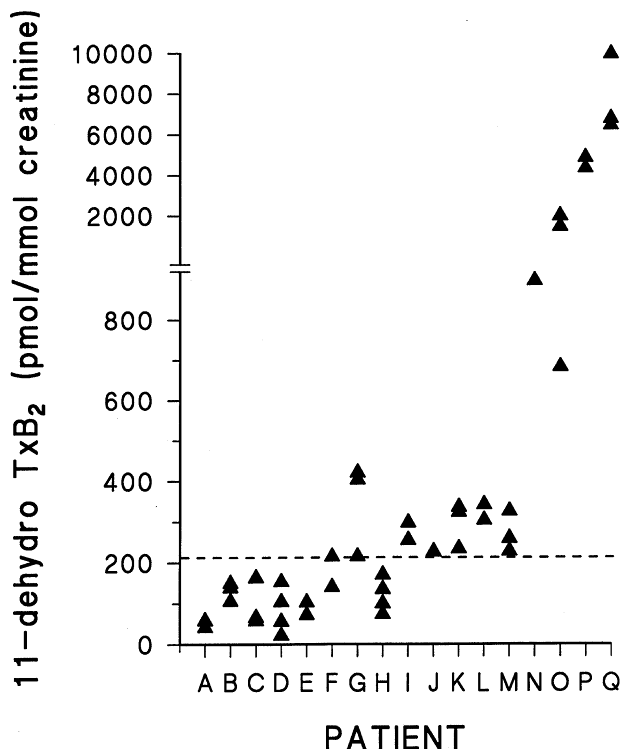

Figure 1. Urinary levels of 11-dehydro-TxB_2 are increased in the majority of 17 patients with mastocytosis. Each patient is denoted by a letter which corresponds to the clinical and histologic data noted in **Table I**. Each *triangle* represents a different 24 h urine collection for a particular patient. The *horizontal dashed line* represents the upper limit of normal (2 SD above the mean) for the urinary excretion of 11-dehydro-TxB_2.

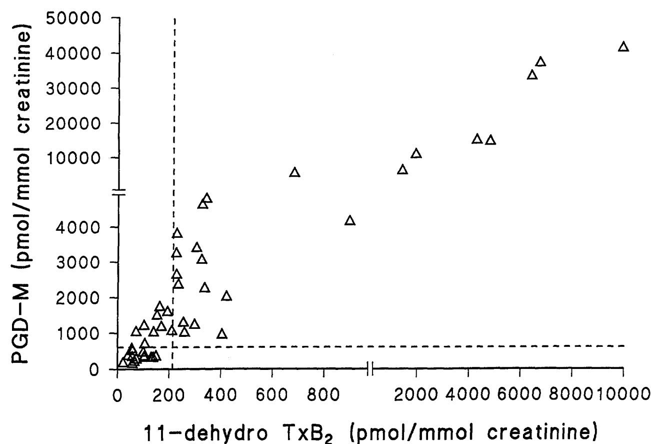

Figure 2. Comparison of the urinary excretion of 11-dehydro-TxB_2 to PGD-M in patients with mastocytosis. Each *triangle* represents a different 24 h urine collection for a particular patient with mastocytosis. The vertical and horizontal dashed lines represent the upper limits of normal for 11-dehydro-TxB_2 and PGD-M, respectively. Urinary levels of both compounds were quantitated by GC/NICI MS assays. The correlation coefficient for the relationship, $r = 0.98$, $r^2 = 0.95$, $p < 0.0001$.

Figure 3 compares the levels of 11-dehydro-TxB_2 and N^{τ}-methylhistamine for the urine samples shown in **Fig 1**. The vertical and horizontal dashed lines represent the upper limits of normal values for 11-dehydroTxB_2 and N^{τ}-methylhistamine, respectively. Again, increases in the urinary excretion of 11-dehydro-TxB_2 are highly associated with and proportional to increases in levels of N^{τ}-methylhistamine in the same samples ($r = 0.91$, $r^2 = 0.84$, $p < 0.0001$).

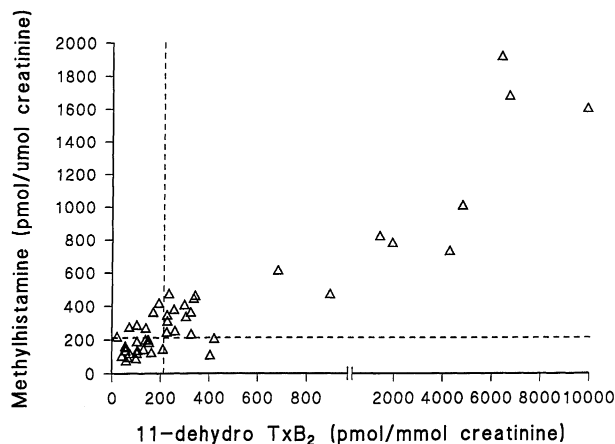

Figure 3. Comparison of the urinary excretion of 11-dehydro-TxB_2 to N^{τ}-methylhistamine in patients with mastocytosis. Each *triangle* represents a different 24 h urine collection for a particular patient with mastocytosis. The vertical and horizontal dashed lines represent the upper limits of normal for 11-dehydro-TxB_2 and N^{τ}-methylhistamine, respectively. Urinary levels of both compounds were quantitated by GC/NICI MS assays. The correlation coefficient for the relationship, $r = 0.91$, $r^2 = 0.84$, $p < 0.0001$.

Table II. Plasma platelet factor 4 and β-thromboglobulin levels in three patients with mastocytosis in whom Tx generation was markedly increased

Patient	Platelet factor 4 (IU per ml)[a]	β-thromboglobulin (IU per ml)[b]
N	4	15
P	8	26
Q	6	16

[a]Normal plasma platelet factor 4 levels are 0–25 IU per ml.
[b]Normal β-thromboglobulin levels are 10–40 IU per ml.

Levels of platelet factor 4 and β-thromboglobulin in plasma of patients with mastocytosis are not increased Although Tx generation is significantly increased in the majority of patients with mastocytosis, the cellular source of this eicosanoid is unknown. It has been previously reported that rat peritoneal and human leukemic mast cells produce prodigious amounts of TxB_2 *ex vivo* (Roberts *et al*, 1979; Macchia *et al*, 1995). The fact that increases in the urinary excretion of 11-dehydro-TxB_2 in patients with mastocytosis correlate closely with both PGD-M and N^{τ}-methylhistamine would support the contention that the source of excessive Tx generation in patients with mastocytosis is the mastocyte. On the other hand, the majority of endogenous Tx formed in normal humans is of platelet origin (FitzGerald *et al*, 1983, 1987). Tx formation is increased *in vivo* in disorders associated with platelet activation including myocardial ischemia, vascular thromboses, and pre-eclampsia, among others (FitzGerald *et al*, 1987). Similarly, other markers of platelet activation are also increased in these diseases, the most frequently measured indices being plasma platelet factor 4 and β-thromboglobulin, which are proteins secreted from platelet α-granules (Nichols *et al*, 1982; Kaplan, 1994). Therefore, we reasoned that if excessive Tx production in patients with mastocytosis is from platelets, then platelet factor 4 and β-thromboglobulin might also be increased. **Table II** shows plasma levels of these two proteins measured in three of the 17 patients with mastocytosis who were studied. All three patients had significantly increased urinary 11-dehydro-TxB_2 excretion. Levels of these markers are normal, in contrast to Tx excretion, supporting the concept that increased Tx generation in patients with mastocytosis is likely not platelet-derived.

Effect of aspirin on suppression and recovery of Tx and PGD_2 formation in patients with mastocytosis We under-

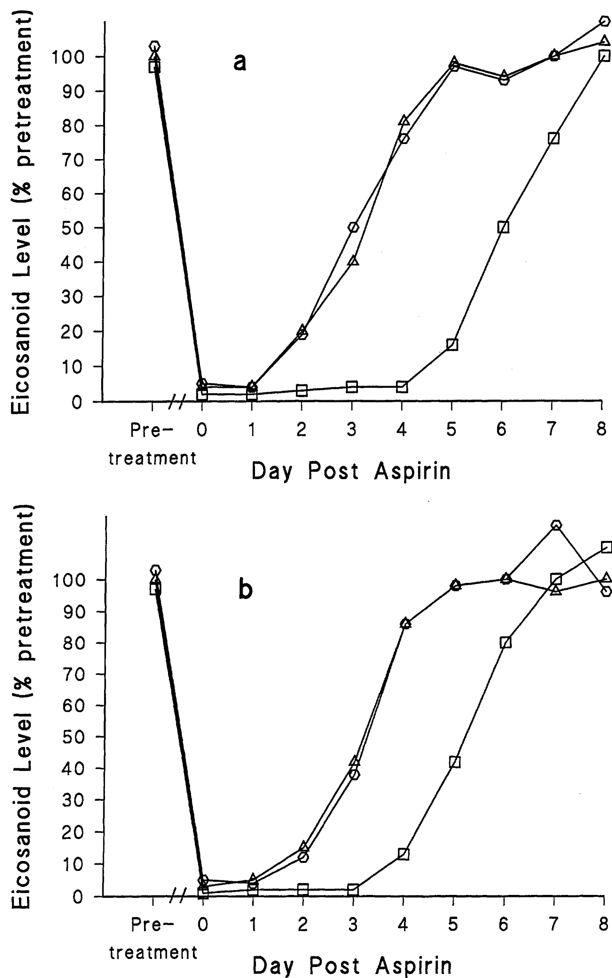

Figure 4. Effect of aspirin treatment on recovery of urinary 11-dehydroTxB$_2$ (△), urinary PGD-M (○), and serum TxB$_2$ (□) in two patients with mastocytosis. Each patient was treated with aspirin 160 mg orally twice a day for 4 d. Therapy was stopped on day 0 and blood and urine collected for the subsequent 8 d. Data for each eicosanoid are expressed percentage pre-aspirin treatment levels. In each patient, pretreatment urinary excretion of both 11-dehydro-TxB$_2$ and PGD-M were markedly increased above the upper limits of normal.

took additional studies to determine the source of excessive Tx production in patients with mastocytosis. Eicosanoid production in human platelets is suppressed for a longer duration than that in other cells by the administration of aspirin *in vivo* likely because the platelet cannot synthesize new cyclooxygenase enzyme, unlike other cellular elements (Campbell and Halushka, 1996). An accurate index of platelet cyclooxygenase activity *in vivo* is the quantitation of serum TxB$_2$ generated *in vitro* by endogenous thrombin activation during whole blood clotting (FitzGerald *et al*, 1983, 1987; Patrono, 1989). We reasoned, therefore, that if the majority of excessive Tx production in patients with mastocytosis is derived from the platelet, the administration of aspirin should affect the pattern of recovery of both platelet TxB$_2$ production and urinary 11-dehydroTxB$_2$ excretion in a similar fashion. If aspirin affected the pattern of recovery of serum TxB$_2$ and 11-dehydro-TxB$_2$ differently, however, this would imply that extraplatelet sources contribute substantially to the excessive 11-dehydro-TxB$_2$ excretion in patients with mastocytosis (FitzGerald *et al*, 1983). We therefore quantitated levels of serum TxB$_2$, and urinary levels of 11-dehydro-TxB$_2$ and PGD-M, daily for 8 d in two individuals with mastocytosis who had been administered aspirin (160 mg twice daily) for 4 d. Both patients had markedly elevated levels of 11-dehydro-TxB$_2$ at baseline. The results are displayed in **Fig 4**(***a***, ***b***). Administration of aspirin suppressed urinary levels of 11-dehydroTxB$_2$, PGD-M, and serum TxB$_2$ > 95% in both patients. Following aspirin treatment, a substantially different pattern of recovery of 11-dehydro-TxB$_2$ is apparent compared with recovery of serum TxB$_2$. Within 1.5 d, levels of 11-dehydro-TxB$_2$ and PGD-M began to increase and returned to pretreatment levels by days 3–4. On the other hand, serum TxB$_2$ levels remained completely suppressed until after day 3 post-treatment and did not recover to near normal levels until 6–8 d post-aspirin therapy.

Table III. Levels of 2,3-dinor-6-keto-PGF$_{1\alpha}$ in four patients with mastocytosis

Patient	2,3-dinor-6-keto-PGF$_{1\alpha}$ (pmol per mmol Cr)[a]	11-dehydro-TxB$_2$ (pmol per mmol Cr)[b]
A	60	59
B	28	150
P	45	4280
Q	39	6720

[a]Urinary levels of 2,3-dinor-6-keto-PGF$_{1\alpha}$ in normal humans are 45 ± 17 pg per mg Cr (mean ± 2 SD).
[b]Urinary levels of 11-dehydro-TxB$_2$ in normal humans are 118 ± 88 pmol per mmol Cr.

Excretion of prostacyclin is not increased in patients with mastocytosis It has been previously reported that in addition to PGD$_2$ and Tx, rat mast cells produce large amounts of PGI$_2$ (Roberts *et al*, 1979). In contrast, however, one report has noted that circulating levels of the PGI$_2$ metabolite, 6-keto-PGF$_{1\alpha}$, are reduced in patients with mastocytosis (Ouwendijk *et al*, 1983), although quantitation of this compound is not an accurate index of systemic prostacyclin generation *in vivo* (Catella *et al*, 1986). Therefore, we quantitated levels of the major urinary metabolite of PGI$_2$, 2,3-dinor-6-keto-PGF$_{1\alpha}$ (Daniel *et al*, 1994), in urine samples from four of 17 patients with mastocytosis to assess whether PGI$_2$ was generated in increased quantities. The results are shown in **Table III**. Two of the patients (A and B) had urinary levels of 11-dehydro-TxB$_2$ that were not elevated and the other two (P and Q) had markedly elevated excretion of the metabolite. As is evident, in all patients, excretion of 2,3-dinor-6-keto-PGF$_{1\alpha}$ was normal.

DISCUSSION

The results of this study provide evidence that systemic Tx production is increased in the majority of humans with mastocytosis. In the patient population that we examined, in which a diagnosis of mastocytosis was carefully documented by both clinical and laboratory examination, 65% of individuals studied had increased excretion of 11-dehydro-TxB$_2$ in at least one urine sample. In addition, increased generation of Tx correlated in a highly significant manner with enhanced formation of two mast cell mediators, PGD$_2$ and histamine. Further, following the administration of aspirin to two individuals with mastocytosis, the recovery of urinary 11-dehydro-TxB$_2$ excretion paralleled that of PGD-M. Taken together, these data suggest that the cellular source of increased Tx formation in patients with mastocytosis could be the mast cell. In this regard, several investigators have reported that TxB$_2$ is a major product of animal or human mast cells stimulated *ex vivo* (Roberts *et al*, 1979; Turner and Dollery, 1988; Undem *et al*, 1990; Macchia *et al*, 1995). In addition, one study has noted an increase in levels of TxB$_2$ in blood from patients with mastocytosis (Ouwendijk *et al*, 1983). Whereas these reports support the contention that the mast cell is the source of increased Tx, other cell types produce this eicosanoid. These include monocytes/macrophages and platelets (Patrono *et al*, 1985; Honda *et al*, 1990; Sanduja *et al*, 1991; Campbell and Halushka, 1996). The vast majority of Tx production in normal humans is believed to be of platelet origin (FitzGerald *et al*, 1983, 1987; Patrono, 1989). Thus, an important issue is whether platelets contribute to the excessive Tx production in patients with mastocytosis. Our studies would suggest this is not the case as other markers of platelet activation, platelet factor 4 and β-thromboglobu-

lin, are not increased in mastocytosis patients with marked overproduction of Tx. In addition, recovery of platelet Tx production after suppression by aspirin is markedly delayed compared with that of urinary 11-dehydro-TxB_2 excretion in humans with mastocytosis. Thus, whereas these observations do not rule out a significant contribution by the platelet to Tx formation in these patients, our findings suggest another cell type is more likely responsible.

In this study, 11 patients had evidence of systemic involvement with mastocytosis. Interestingly, 10 of these 11 individuals (91%) had increased urinary excretion of Tx whereas no patient without evidence of systemic disease had an increased concentration of urinary 11-dehydro-TxB_2. These results suggest that elevated levels of urinary 11-dehydro-TxB_2 may be a predictor of systemic involvement by mastocytosis in humans.

The significance of excessive Tx production in patients with mastocytosis is unclear. TxA_2 possesses a number of potent biologic activities and is likely an important pathophysiologic mediator in certain human diseases (Campbell and Halushka, 1996). Tx induces bronchoconstriction and is believed to play a part in bronchial hyperrepsonsiveness in asthma and acute allergic reactions (Fugimura *et al*, 1991; Ohtsuka *et al*, 1996). Interestingly, whereas dyspnea is unusual in settings of mast cell activation in patients with mastocytosis, a fall in forced expiratory volume in 1 s can usually be documented (Roberts *et al*, 1998). It is, therefore, conceivable that overproduction of Tx might contribute to the bronchoconstriction associated with mast cell activation.

TxA_2 is also a potent vasoconstrictor in a number of vascular beds (Campbell and Halushka, 1996). Although hypotension is frequently associated with mast cell activation in patients with mastocytosis, a subset of individuals become hypertensive (Roberts *et al*, 1998). This has been previously attributed to alterations in the metabolism of PGD_2 with excessive formation of the reduced metabolite $9\alpha,11\beta$-PGF_2, which is a vasoconstrictor (Roberts *et al*, 1998). Alternatively, it is possible that in this subset of patients, excessive Tx production could contribute to the hypertension. In addition, TxA_2 has been reported to be a potent mitogen and induce cellular proliferation (Sachinidis *et al*, 1995; Palaka *et al*, 1997). Whether excessive production of Tx in mastocytosis contributes to mast cell proliferation is unknown.

In addition to quantitating Tx production, we also sought to determine whether PGI_2 formation was enhanced in patients with mastocytosis. As noted, in four patients that we studied, we were unable to document increases in this mediator, suggesting that excessive prostacyclin production does not contribute to the pathophysiology of mastocytosis.

In summary, we report that Tx production is significantly increased in the majority of patients with mastocytosis that we studied. The cellular source of this eicosanoid is unknown but it does not appear to be of platelet origin. Experiments aimed at definitively determining the cell responsible for excessive Tx production in patients with mastocytosis will aid in future studies designed to elucidate the role of this eicosanoid in the pathophysiologic sequelae of mast cell activation.

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