

Case study

Systemic mastocytosis associated with acute myeloid leukemia: Case report and implications for disease pathogenesis

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Mastocytosis may be associated with clonal nonmast cell lineage hematologic diseases, including myelodysplastic syndromes, myeloproliferative disorders, and acute myeloid leukemia. Here we present a patient with the simultaneous diagnosis of mastocytosis and an acute myeloid leukemia, M2 subtype in the French-American-British classification, with t(8;21) carrying a population of immature mast cell precursors, and discuss this presentation in the context of a potential pathogenetic cellular link between this leukemia and mastocytosis. (*J Allergy Clin Immunol* 2004;114:28-33.)

Key words: Mast cell, mastocytosis, acute myeloid leukemia

CASE PRESENTATION

A 67-year-old woman consulted on April 1999 because of a 4-month history of fatigue, ecchymosis, and spontaneous hematomas in the absence of pruritus, flushing, abdominal pain, or diarrhea. Physical examination was unremarkable except for the presence of ecchymosis and hematoma in the absence of other skin lesions. Peripheral blood analysis revealed the existence of a moderate normocytic anemia (hemoglobin, 96 g/L) and thrombocytopenia (16×10^9 platelets/L; normal values, $150\text{--}350 \times 10^9$ /L) associated with a leukocytosis of 25×10^9 cells/L (normal values, $4.5\text{--}10.5 \times 10^9$ /L) with 71% blast cells containing a few azurophilic granules and, in some cells, Auer rods. No circulating mast cells (MCs) were observed in microscopic examinations. An increased

Abbreviations used

AHNMD: Clonal non-MC lineage hematologic disease
AML: Acute myeloid leukemia
BM: Bone marrow
CR: Complete remission
FAB: French-American-British
MC: Mast cell
MDS: Myelodysplastic syndrome
MPD: Myeloproliferative disorder
NHL: Non-Hodgkin lymphoma
SM: Systemic mastocytosis

serum tryptase of 58 ng/mL was detected at diagnosis. Coagulation tests and routine blood chemistry studies were within the normal range except for a moderate increase in lactate dehydrogenase (476 IU/L; normal values, 80-460 IU/L).

Initial morphologic examination of a bone marrow (BM) aspirate was performed at presentation and revealed an infiltration of 59% myeloid blast cells, with 35% and 59% positive for chloroacetate esterase and peroxidase, respectively. No dysplastic features were seen in mature neutrophils, megakaryocytes, or erythroblasts. Further examination revealed atypical MCs exhibiting elongated cytoplasmic extensions, eccentric oval nuclei, and a hypogranulated cytoplasm with focal granule accumulation (Fig 1, A). MCs stained strongly for both chloroacetate esterase and toluidine blue (Fig 1, B). A minority of the blast cells (1.3%) also exhibited metachromatic granules as assessed by toluidine blue staining. The patient was diagnosed as having acute myeloid leukemia (AML), M2 subtype in the French-American-British (FAB) classification.¹ In addition, the coexistence of a BM mastocytosis was suspected.

After premedication with H1 and H2 antihistamines, induction treatment for AML with idarubicin plus cytarabine (ARA-C) according to the PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) 99 protocol for persons older than 65 years² was initiated within the intensive care unit. Five weeks after the completion of induction chemotherapy, a BM biopsy was performed together with a complete

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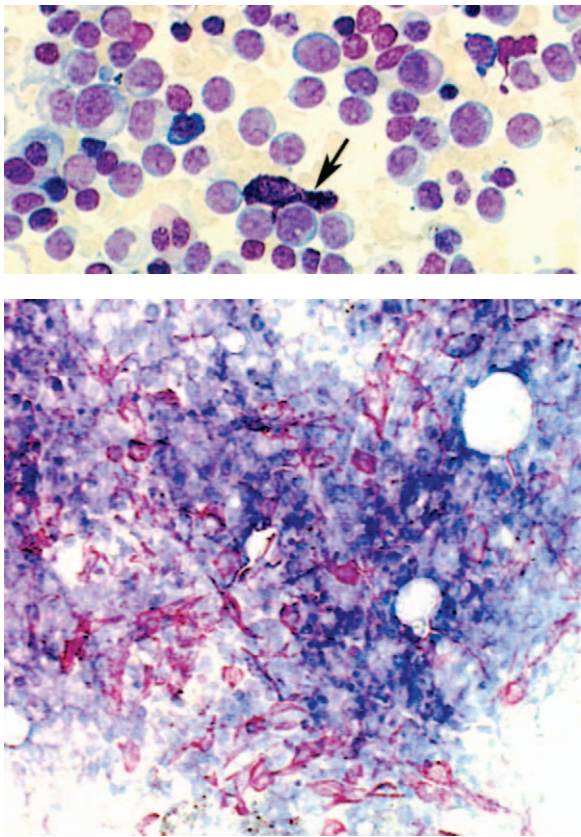


FIG 1. A, May-Grünwald Giemsa-stained BM smear at diagnosis showing a massive infiltration by myeloid blast cells and an abnormal MC (arrow) with spindle shape, cytoplasmic prolongations, and oval nucleus. **B,** Toluidine blue staining revealed a dense compact aggregate of spindle-shaped MCs in a BM particle.

immunophenotypic study to confirm the suspected coexistence of systemic mastocytosis (SM). Microscopic examination showed a partial response with persistence of 6% blasts and abnormal MCs. A second identical cycle of chemotherapy was then administered, and morphological complete remission (CR) was obtained. Intensification chemotherapy with ARA-C plus idarubicin according to the PETHEMA 99 protocol was administered. This continued until September 1999 (month +6). At this time, the patient was in morphological CR with 1.8% residual leukemic blasts by phenotype in the BM and persistent abnormal MCs. The serum tryptase was now normal (6.29 ng/mL).

One year later, in September 2000, the patient was found to have a thrombocytopenia of 21×10^9 platelets/L. A BM analysis showed a relapse with an infiltration of 54% blast cells with characteristics identical to those of blasts observed at diagnosis. Induction chemotherapy with mitoxantrone and ARA-C plus etoposide derivative (VP-16) was then administered. A BM examination after this cycle showed morphological CR with <1% blasts by phenotype. Consolidation therapy consisting of ARA-C plus 6-thioguanin followed through January 2001 (month +21).

In July 2001 (month +27), the patient developed a second relapse. Despite further chemotherapy with

TABLE I. Distribution of BM MCs, myeloid blast cells, and MC-lineage committed blasts at diagnosis and during follow-up

	Clinical status	% AML blast cells	% CD117 ⁺⁺⁺ blast cells	% of CD25 ⁺ CD117 ⁻ MC/ % of CD25 ⁻ CD117 ⁺ MC	
				% MC	
Diagnosis		59	NA	NA	NA
Day +42	Partial response	6	0.08	0.16	100/0
Month +5	CR	1.8	1	0.13	30/70
Month +6	CR	1	0.10	0.05	70/30
Month +10	CR	1	<0.01	0.17	70/30
Month +15	Second relapse	18	0.08	0.14	68/32
Month +18	Progressive disease	28	0.19	0.05	100/0

NA, Not analyzed.

ARA-C plus 6-thioguanin, the patient did not reach a morphological CR and died on April 2002 as a result of sepsis.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses considered in this case included non-MC tryptase-positive hematopoietic neoplasms, mastocytosis associated with clonal non-MC lineage hematologic diseases (AHNMDs), and other pathologic conditions associated with an increase in BM MCs.

LABORATORY AND OTHER TESTING AND PROCEDURES

The results of the immunophenotypic studies performed at diagnosis and during follow-up are summarized in **Tables I and II**. As may be seen in **Table I**, as many as 2 different populations of blast cells in addition to MCs were detected in the BM, their relative distribution varying between samples obtained at different time points. Phenotypically, at diagnosis, blast cells showed expression of myeloid-associated markers (CD13⁺, CD33⁺, CD117⁺, MPO^{-/+}) in the absence of lymphoid-related antigens (cCD79a⁻, cCD3⁻) except CD7 and CD19, which were partially expressed. Most blast cells displayed an immature CD34⁺⁺ phenotype, whereas a small fraction of these cells showed maturation toward the MC lineage (tryptase-positive, FcεRI^{-/+}, CD117⁺⁺⁺, CD34^{-/+}, HLA-DR^{-/+}; **Table II**).

Conventional cytogenetic analysis revealed a normal 46,XX karyotype. Despite this, interphase fluorescence in situ hybridization demonstrated the presence of *AML-1/ETO* gene rearrangements -t(8;21)(21q22)- (Vysis, Downers Grove, Ill) in blast cells in the absence of *BCR/ABL* (dual color, dual fusion *BCR/ABL* probe; Vysis) translocation. A specific immunophenotypic analysis of MCs was not performed at this time.

TABLE II. Immunophenotypic characteristics of myeloid blast cells and MCs*

	Myeloid blast cells	CD117 ⁺⁺⁺ blast cells	CD25 ⁺⁺ MCs	CD25 ⁻ MCs
CD2	—	—	+	—
CD3	—	—	—	—
cCD3	—	—	—	—
CD5	—	—	—	—
CD7	—/+ (25%)	—	—	—
CD13	+	+	++	+
CD14	—	—	—	—
CD15	—	—	—	—
CD18	—	+	++	+
CD19	—/+ 53%	—/+ 36%	—	—
CD25	—	—/++ (23% to 77%)†	++	—
CD28	—	—	—	—
CD33	+	+/++	+/+++	++
CD34	++	—/+ (17% to 100%)†	—	—
CD35	—	—	++	—
CD36	—	—	—	—
CD38	+	+	—	—
CD45	+	+/++	++	++
CD50	—	—	++	+
CD54	—	—	+	—/+ (14%)
CD56	—/+ 77%	—/+ 23%	—	—
CD58	+	—	+	—
CD59	+	++	+++	++
CD61	—	—	—	—
CD63	+	++	+++	++
CD64	—	—	—	—
CD65	—	—	—	—
CD69	+	+/++	+++	++
CD71	+	+	—	—
cCD79a	—	—	—	—
CD88	—	—	+	—
CD117	++	+++	+/+++	+++
CD123	+	+	+	—
CD163	—	—	—	—
β-2	++	—	+++	++
Microglobulin	—	—	—	—
c Tryptase	—	+/++	+/+++	+++
FcεRI ⁻	—	—/++ (72%)	+/+++	++
cBcl-2 ⁺	—	+/++	+/++	+/++
HLA-DR ⁺	+	—/+ (38%)	—	—
cMPO	—/+ (9%)	—	—	—
nTDT	—	—	—	—

c, Cytoplasmic; n, nuclear; MPO, myeloperoxidase; TDT, terminal deoxynucleotidyl transferase.

*Results expressed semiquantitatively as —, negative; +, dim positive; ++, intermediate; and +++, strong expression. For cell populations showing partial expression of individual markers, the percentage of positive cells is shown in parentheses.

†Changes in the percentage of positive cells for this marker were observed during follow-up.

After initial induction chemotherapy (day +42), BM histology showed a normal cellularity with 6% blast cells phenotypically identical to those detected at diagnosis. This finding was associated with a moderate increase in strongly tryptase-positive MCs and modest perivascular MC aggregates. Neither fibrosis nor an admixture of other cells such as lymphocytes or eosinophils was observed. Immunophenotypic analysis using conventional flow cytometry³⁻⁵ confirmed the presence of 0.07% MCs. All MCs displayed aberrant expression of CD2 and CD25 (Fig 2) in association with overexpression of CD35, CD59, and CD69^{6,7} (Table II). In addition, a subset of CD117⁺⁺⁺ blast cells with low sideward light scatter coexpressed FcεRI, tryptase, and CD25 in the absence of reactivity for the CD2 antigen (Fig 2). This phenotype is highly suggestive of cells committed toward the MC lineage (Table II). The relative distribution of these MC precursors as well as myeloid blast cells during follow-up is shown in Table I. Phenotypically aberrant MCs were consistently detected in follow-up samples, whereas the presence of myeloid blast cells, including blasts phenotypically committed toward the MC lineage, could be clearly identified only in samples that did not show a morphological CR. Interestingly, this later population of CD117⁺⁺⁺/low sideward light scatter MC-committed blasts coexpressing CD34 and HLA-DR could also be detected at the time of the second relapse in peripheral blood. However, in contrast to their BM counterpart, these cells lacked the expression of FcεRI.

The somatic activating mutation at codon Asp816Val of *c-kit* (exon 17 of *c-kit* gene) was not found on purified populations.⁸

DIAGNOSIS WITH DISCUSSION OF PATHOGENESIS

A MC hyperplasia within BM may be observed in pathologic conditions other than mastocytosis, including Hodgkin disease,^{9,10} non-Hodgkin lymphoma (NHL),¹¹⁻¹⁴ and myelodysplastic syndromes (MDSs).^{15,16} In such diseases, MC morphology is normal, and compact MC aggregates are not present.¹⁷ Moreover, BM MCs display a normal immunophenotype, lacking expression of both CD2 and CD25.^{6,18}

An increase in serum tryptase levels has been described in ~40% of patients with AML^{19,20} and in a variable number of cases with MDSs.¹⁶ In most of these patients, no involvement of the MC lineage is found when morphological criteria are used.^{16,21,22}

Myelomastocytic syndromes, which include myelomastocytic leukemia and myelodysplastic MC syndrome, are characterized by a marked increase in immature metachromatic blasts, which typically represent >10% of all nucleated cells in the BM or peripheral blood of patients with myeloid malignancies.²²⁻²⁶ These blast cells show reactivity for both c-Kit and tryptase but lack expression of CD2 and CD25. These cells also do not exhibit the Asp816Val *c-kit* mutation.^{22,24} Furthermore,

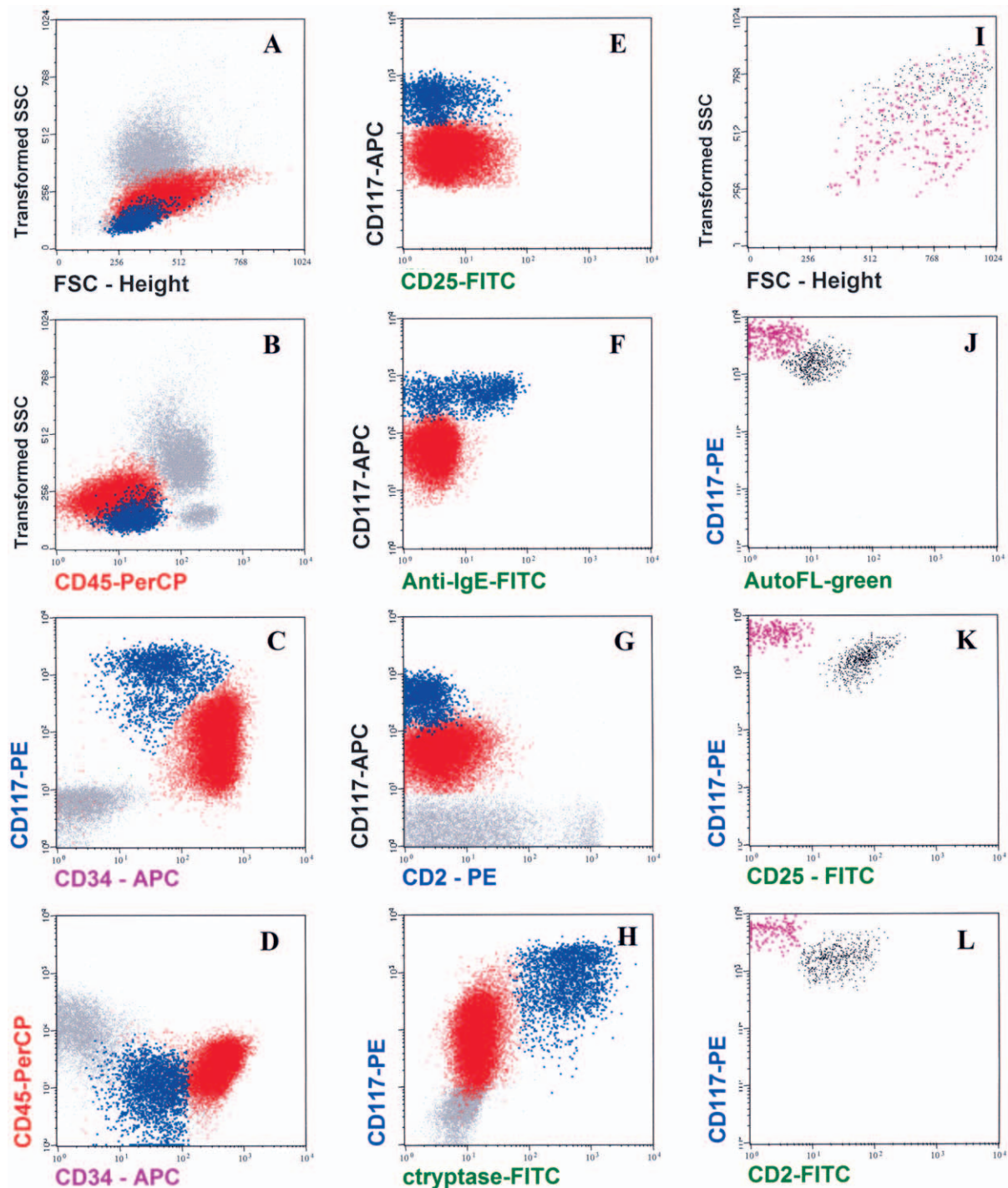


FIG 2. Representative immunophenotypic characteristics of myeloid blast cells and MCs coexisting in the patient's BM. **A-H,** Myeloblasts. Note the presence of a small population of blast cells showing an immature ($CD34^+/CD45^+$) phenotype, suggesting commitment toward the MC lineage ($CD117^{+++}$, tryptase-positive, $Fc\epsilon R1^{-/+}$, $CD25^{-/+}$; blue dots) in contrast with a major population of non-MC $CD34^{++}$ leukemic blast cells (red dots). **I-L,** $CD117^{+++}$, selectively gated BM MCs from the same patient. In these panels, black dots correspond to $CD25^{++}$, $CD2^+$ aberrant mast cells and violet events to normal mast cells. APC, Allophycocyanine; tryptase, cytoplasmic tryptase; FITC, fluorescein isothiocyanate; PE, phycoerythrin; PerCP, peridinin chlorophyll protein.

BM MCs from these patients do not meet the morphologic criteria for SM.^{24,27} Response to polychemotherapy with CR has been reported in 1 case.²³

Mastocytosis associated with an AHNMD²⁸⁻³⁰ is included as a specific variant of mastocytosis in current classification schemes.^{24,31} Following recently established consensus criteria, the diagnosis of SM-AHNMD implies that criteria for the diagnosis of both SM²⁴ and an AHNMD (FAB/World Health Organization criteria)^{1,32-35} are fulfilled. Such criteria are of special relevance in the diagnosis of MDSs and myeloproliferative disorders (MPDs). Accordingly, a careful morphologic and histologic examination of BM in mastocytosis has revealed the frequent coexistence of discrete features of MPD or MDS. However, in most of these situations, the criteria to diagnose MPD or MDS are not fulfilled. In many cases, the diagnosis of both MS and AHNMD is coincidentally made. In other patients with mastocytosis, a second hematologic disease subsequently becomes evident after a variable period.^{21,29,30,36-41}

Despite the publication of an increasing number of patients with SM, including SM-AHNMD, the relationship between the 2 coexisting clonal disorders in these latter patients remains to be elucidated fully.

Some recent publications report that the Asp816Val *c-kit* mutation may be present in different hematopoietic cell lineages,⁴²⁻⁴⁵ including a subgroup of patients with SM who have smoldering mastocytosis. This observation supports the possibility that this disease involves a hematopoietic progenitor capable of differentiating into both myeloid and lymphoid cells. Previous studies have also demonstrated the presence of *c-kit* mutations in indolent SM as well as in SM-AHNMD in hematopoietic cell compartments other than MCs.⁴²⁻⁴⁵ However, in these latter patients, the Asp816Val *c-kit* mutation is not always found in both the non-MC hematologic neoplasm and the clonal MC population. For example, a patient with an Asp816Val *c-kit* mutation-positive SM has been reported who developed a T-cell leukemia negative for this mutation.⁴²

In the patient reported here, we were unable to demonstrate the presence of the Asp816Val *c-kit* mutation. *AML-1/ETO* gene rearrangements were detected in the leukemia myeloid blast cells, some of which showed maturation toward the MC lineage. However, we could not demonstrate the presence of t(8;21) in the mature aberrant MCs. This prevents us from making a definitive conclusion about the relationship between myeloid blast cells and mature aberrant MCs.

FINAL DIAGNOSIS WITH TREATMENT AND MANAGEMENT PLANS

In the case reported here, the diagnosis of mastocytosis was confirmed on the basis of 1 major criterion (presence of BM MC aggregates) and 2 minor criteria (morphologically abnormal MCs carrying an aberrant immunophenotype) according to the World Health Organization classification. The small size of BM MC aggregates could

be explained by the fact that BM biopsy was performed after a cycle of idarubicin plus ARA-C and response of SM to cytoreductive therapy. In fact, in BM samples studied once the patient achieved morphological CR, the number of phenotypically aberrant MCs was clearly reduced.

An identical response of aberrant MCs to chemotherapy has been reported in a case of SM associated with an NHL. This patient was treated with cladribine.⁴⁶

The criteria for the diagnosis of AML (FAB M2) with t(8;21) were fulfilled in this patient. Thus, as proposed in the consensus classification, the patient was diagnosed as SM-AHNMD of the AML subtype.

In patients with SM-AHNMD, the therapeutic approach selected depends on the clinical form of the disease. As in AHNMD, treatment of mastocytosis should be selected on the basis of the existing database of possibilities⁴⁷⁻⁵⁰ (see Valent et al in this issue). In the current case, specific treatment for mastocytosis was not necessary. There was an absence of symptoms related to MC mediator release and a low MC burden. The specific treatment for AML appropriate to age and performance status of the patient was indicated and given.

SUMMARY

Mastocytosis may be associated with non-MC lineage hematologic disorders including AML, MDS, MPD, and NHL.²¹ Among all patients diagnosed with these non-MC lineage hematologic disorders, a few are found to coexist with mastocytosis. Thus, care should be taken in the morphological BM examination to rule out the presence of abnormal MCs. If SM is suspected, a careful histologic and immunophenotypic analysis of MCs is mandatory. Analysis of serum tryptase may help to confirm the coexistence of SM. Specifically, in the case here reported, immunophenotyping, apart from confirming the pathologic nature of MC, revealed the presence of a subset of myeloid blast cells displaying features consistent with differentiation into the MC lineage. However, we were not able to demonstrate the presence of a common mutation or cytogenetic abnormality in both cell compartments. Further research is necessary to determine the relationship between the MCs and other hematologic neoplastic cells in SM-AHNMD, in part through the demonstration of a common genetic abnormality in both cell compartments.

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