

Neuroinflammatory disorders and mastocytosis: A possible association?



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Clinical Implications

- As experimental data show that mast cells are involved in neuroinflammation, we present 9 patients with mastocytosis and neuroinflammatory disorders such as multiple sclerosis, optic neuritis, or pachymeningitis, with 2 successes of mast cell–targeting treatments in controlling neurological symptoms.

TO THE EDITOR:

Mastocytosis is a disorder characterized by mast cell proliferation and accumulation within various organs.¹ Psychiatric and neurological symptoms are frequent in mastocytosis, occurring in approximately 25% of patients.^{2,3} In the meantime, experimental data converge to describe involvement of mast cells in multiple sclerosis.⁴ Therefore, it is tempting to hypothesize that in diseases in which mast cells are in excess as in mastocytosis, there may be an excess of neurological manifestations including nerve tissue inflammation and neuropsychiatric symptoms.

To test this hypothesis, we conducted a retrospective observational study in the French reference center for mastocytosis (centre de référence des mastocytoses [CEREMAST]) by screening for patients with mastocytosis presenting with neurological symptoms suggesting neural inflammation that have required further explorations including magnetic resonance imaging (MRI) and/or cerebrospinal fluid (CSF) analysis.

Patients were found by keyword search in our electronic database comprising 600 patients with mastocytosis in the skin, cutaneous mastocytosis, indolent systemic mastocytosis, systemic mastocytosis with associated hematologic neoplasm, smoldering systemic mastocytosis, and mast cell leukemia¹ using the following entries: “multiple sclerosis,” “retrobulbar optic neuritis,” “neurological,” and “posterior uveitis” (see Figure E1 in this article’s Online Repository at www.jaci-inpractice.org). To be retained, patients had to present neurological, ophthalmic, or psychiatric symptoms, which were explained by either a defined neuroinflammatory condition (multiple sclerosis confirmed by 2010 MacDonald revised criteria,⁵ posterior uveitis, retrobulbar optic neuritis, or noninfectious meningitis), or associated with MRI or CSF anomalies concordant with inflammation when all alternative diagnoses had been excluded.

Of 600 patients registered in the CEREMAST Paris center, 34 patients were initially screened, 25 were subsequently

excluded because they had no objective neurological symptoms found by specialist assessment (n = 9), no MRI or CSF analysis (n = 10), or anomalies explained by a differential diagnosis (n = 5), or unproven mastocytosis (n = 1). Nine patients were finally studied (Table 1). Mean ages at mastocytosis and neurological symptoms onset were 41 and 52 years, respectively. Indolent systemic mastocytosis (n = 3), mastocytosis in the skin (n = 3), cutaneous mastocytosis (n = 1), smoldering systemic mastocytosis (n = 1), and systemic mastocytosis with associated hematologic neoplasm (n = 1) were represented. D816V mutation prevalence was 78% (7 of 9). Symptoms linked to neuroinflammation occurred after mastocytosis onset (n = 7), or simultaneously (n = 1), or before mastocytosis onset (n = 1). They could be progressive (n = 5), paroxysmal (n = 2), or remittent (n = 2).

Neurological symptoms (n = 5) were sensory (n = 3, limb paresthesias) or motor (n = 4, gait disorders with upper motor neuron signs). Ophthalmologic conditions (n = 2) were represented by relapsing posterior uveitis with choroiditis and meningitis (n = 1), and by bilateral optic neuritis (n = 1). Psychiatric features (n = 2) included olfactory and gustative stimuli–induced panic attacks (n = 1) and ictal aggressiveness (n = 1).

Representative images are shown in Figure 1. Both cerebral (n = 9) and neural spine (n = 1) T2 fluid-attenuated inversion recovery hypersignals were present. The most frequent locations were juxtaventricular (n = 5) and subcortical (n = 4). Temporal dissemination was present in 3 cases. Unexplained pachymeningitis in an invasive smoldering systemic mastocytosis context was elicited in 1 patient.

Lumbar puncture had been performed in 5 patients. The most frequent CSF anomalies were oligoclonal bands (n = 4) and lymphocytic meningitis (patient 1, uveomeningitis). In 2 cases, electromyography was performed and was normal. Evidence for peripheral nervous involvement was present in 1 patient (patient 10) (abolished sympathetic reflexes and small-fiber neuropathy on skin biopsy). For this patient, no other evident cause of small-fiber neuropathy was found.

Prednisone was used in 4 cases (1 success patient 1, 1 partial response patient 2, 2 failures patients 4 and 8). Rapamycin was used for patient 9, with partial response (incomplete improvement of cognition, fatigue, and pain). Masitinib trials were unsuccessful (n = 2). Patient 7 had a partial response to omalizumab 150 mg weekly. Antidepressants were efficient for patient 5 but failed for patient 9, who responded to rapamycin.

Our series describes the occurrence of inflammatory neurological lesions among 9 patients with mastocytosis. Three cases of multiple sclerosis associated with mastocytosis had already been reported² and here we report 4 additional cases (Table 1). We also report for the first time evidence of small-fiber neuropathy with no other cause than mastocytosis in 1 patient.

The remaining patients presented with atypical and unclassified clinical symptoms that could impede the clinician from evoking an inflammatory neurological process. One patient with anxiety experienced repeated panic attacks associated with flushing and itching. These attacks were triggered by various stimuli including aliments and olfactory stimuli, which are

TABLE I. Characteristics of the 11 patients with neuroinflammatory lesions and mastocytosis

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Sex	F	M	M	M	F	M	F	F	M
MCD/NID diagnosis	MIS RRMS	ISM PPMS	MIS RBN	ISM PPMS	CM (TMEP) Unclassified	SSM Pachymeningitis	ISM Unclassified	SM-AHN PPMS	MIS Unclassified
Major MCD symptoms	UP	Flushing, itching, diarrhea	Flushing, itching, diarrhea	UP	Abdominal pain, flushing, itching,	UP, weight loss, and asthenia	UP, flushing, abdominal pain	UP, diarrhea, myalgias, osteopenia	UP, flushes, myalgias, osteoporotic vertebral fracture
Major neurological symptoms	Relapsing posterior uveitis	Progressive gait disorder	Remittent optic neuritis	Progressive gait disorder and lower limbs hypoesthesia	Panic attacks triggered by gustative and olfactive stimuli	Progressive gait disorder, new-onset headaches	Attacks of aggressivity with ictal amnesia	Progressive right hemibody motor deficit and paresthesias	Progressive inferior limbs paresthesias, proprioceptive ataxia
Supratentorial hypersignals	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes
Brain stem hypersignals	No	Yes	No	Yes	No	Yes	No	ND	No
Cervical or thoracic spine hypersignals	No	No	ND	Yes	ND	No	No	ND	No
Temporal dissemination	Yes	No	ND	Yes	No	ND	Yes	ND	ND
CSF analysis	Lymphocytic meningitis	Oligoclonal bands	ND	Oligoclonal bands	Oligoclonal bands	ND	ND	Oligoclonal bands	ND
Miscellaneous		Altered somesthetic and motor potentials		Normal EMG				Small- fiber neuropathy (skin biopsy)	

CM, Cutaneous mastocytosis; F, female; ISM, indolent systemic mastocytosis; M, male; MCD, mast cell disorder; ND, not done; NID, neuroinflammatory disorder; PPMS, primary progressive multiple sclerosis; RBN, retrobulbar neuritis; RRMS, relapsing remittent multiple sclerosis; SSM, smoldering systemic mastocytosis; TMEP, telangiectasia macularis erupta perstans; UP, urticaria pigmentosum.

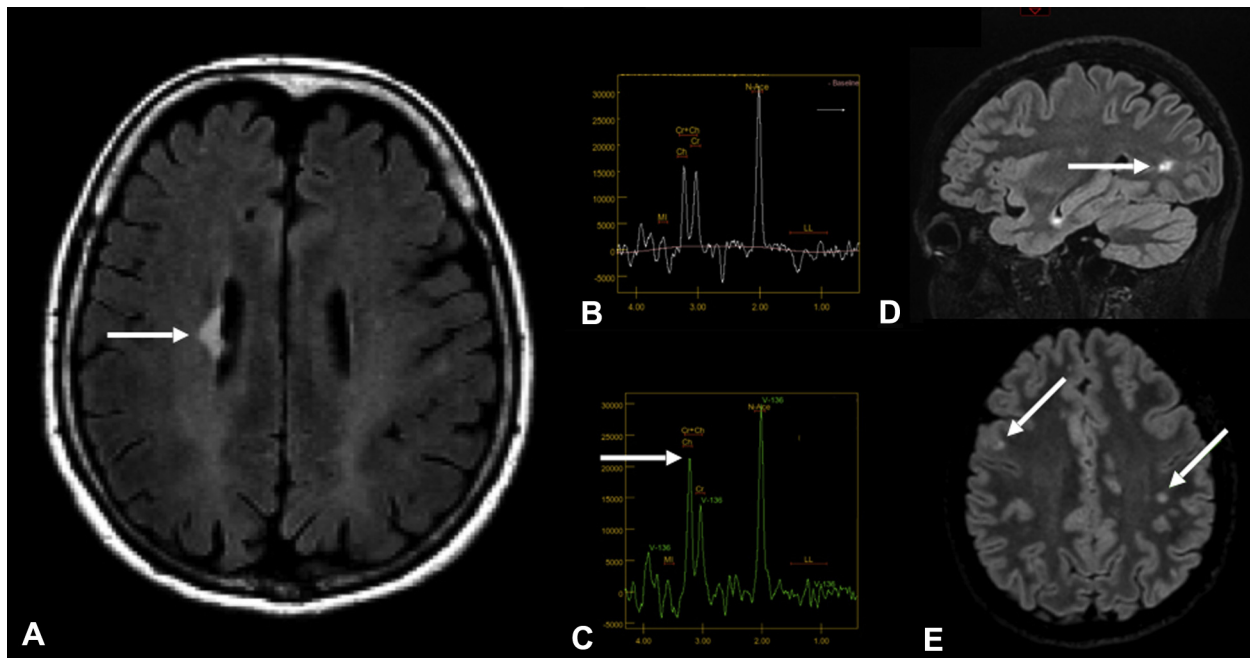


FIGURE 1. Examples of magnetic resonance neuroinflammatory anomalies. Patient 5: Atypical leucopathy (A), with a magnetic resonance spectroscopy centered on the lesion (C) showing a prominent pick of increased choline compared with a normal spectrum (B). Patient 1: Subcortical fluid-attenuated inversion recovery hyperintensities (D and E).

common mast cell degranulation inducers. Interestingly, this patient presented an atypical leucopathy with a choline peak in MRI spectroscopy (Figure 1). Another patient underwent daily crises of sudden aggressiveness with ictal amnesia. Juxtacortical and juxtaventricular inflammation-evoking MRI hypersignals were localized in her left frontal cortex. Ictal aggressiveness has previously been linked to epilepsy in these regions.⁶ Symptoms were not triggered by mast cell degranulation stimuli, but were relieved by omalizumab, an anti-IgE antibody that inhibits mast cell activation.⁷

Altogether, these observations make us believe that neuroinflammation may be underestimated during mastocytosis because of protean manifestations and quick classification of symptoms into the neighboring entity of mast cell activation syndrome. For example, diffuse paresthesias are often linked to mast cell activation syndrome, but our data suggest that it could either be caused by central inflammatory lesions or even by small-fibers neuropathy (patient 8). However, in these cases, we could not rule out that mast cells may have initiated or amplified this inflammatory process.

Regardless of the direct or indirect role of mast cells, treatments aiming at reducing their activity could help to spare the use of corticosteroids. In this regard, improvement in disease symptoms was observed using omalizumab in one patient (patient 8) and rapamycin, which inhibits mast cell growth and activation,⁸ in another (patient 9). Surprisingly, serotonergic reuptake inhibitors induced a complete response in 1 patient (patient 5), suggesting that nerve-targeting treatments can modulate the whole mast cell-glial cell-neuron unit.

Our study is limited by the heterogeneity of mastocytosis diagnoses in our cohort and by the absence of histological proof of abnormal mast cell infiltrate in the brain and absence of mast cell mediators measurement in CSF. Multiple sclerosis prevalence during mastocytosis seems higher than in the general French population (4/600 vs 97.5/100,000⁹), although our study is not designed to prove it.

In conclusion, we present a series of 9 patients with mastocytosis and concomitant neuroinflammatory disorders, which raises the question of involvement of abnormal mast cells in human neuroinflammation.

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

P. Dubreuil is a shareholder and consultant for AB Science, which develops mastitinib. O. Hermine serves as President of the Scientific Committee of AB Science. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 6, 2019; revised March 29, 2019; accepted for publication April 12, 2019.

Available online May 8, 2019.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.04.033>

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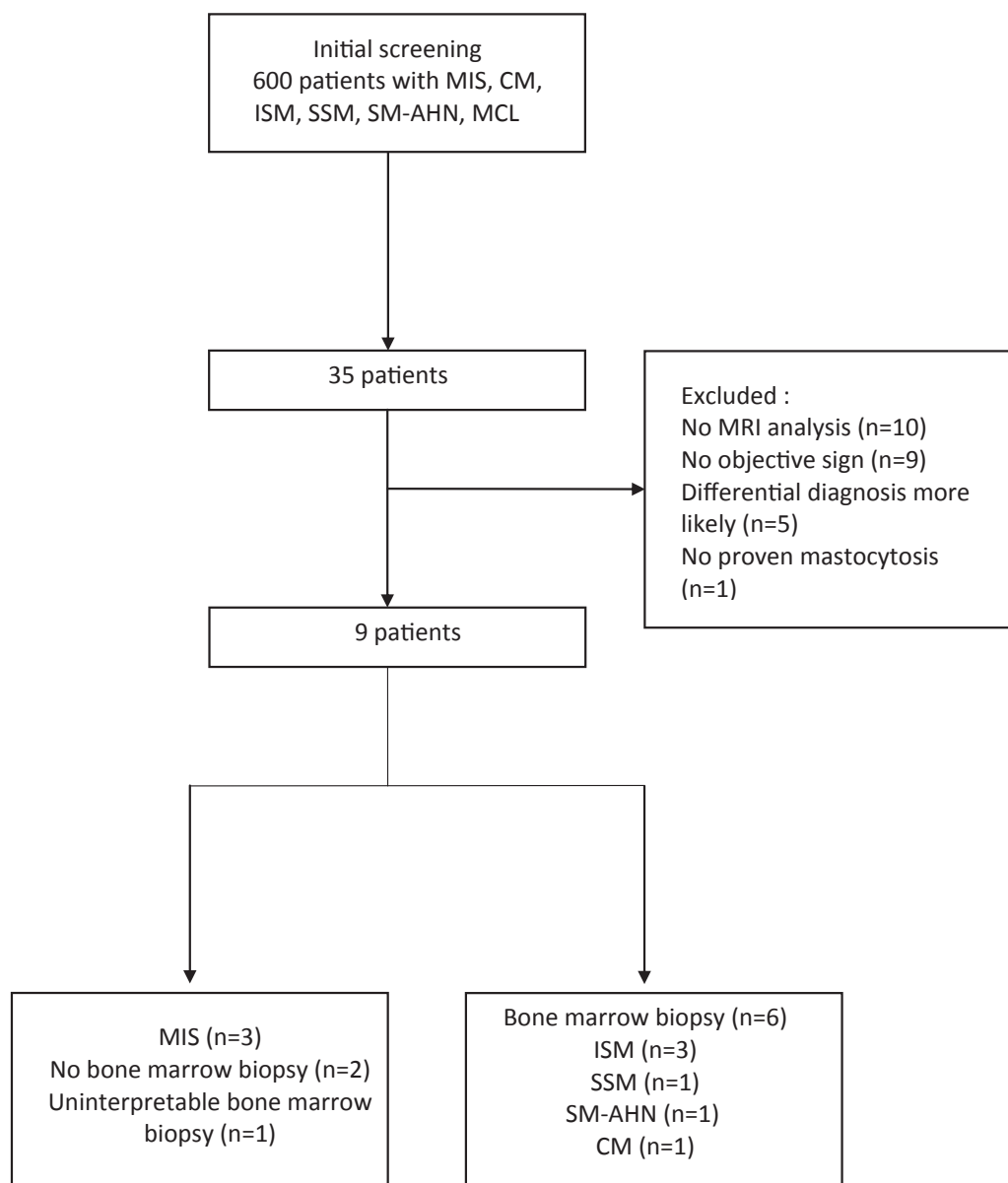


FIGURE E1. Flowchart of patients' screening and final diagnoses of mastocytosis in our cohort. *CM*, Cutaneous mastocytosis; *ISM*, indolent systemic mastocytosis; *MCL*, mast cell leukemia; *MIS*, mastocytosis in the skin; *SM-AHN*, systemic mastocytosis with associated hematologic neoplasm; *SSM*, smoldering systemic mastocytosis.