Journal of Neurological Sciences [Turkish] **31:(2)**# 40; 398-407, 2014
http://www.jns.dergisi.org/text.php3?id=782

Case Report

Frontal Lobe Like Syndrome Due To Bee Sting

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Summary

A 34 year-old male beekeeper experienced flushing, breathing difficulty and loss of consciousness five minutes after he got stung by a honeybee. He was admitted to a local emergency room with hypotension and a phyliform pulse. After a 24-hour period of unresponsiveness, the patient gained consciousness and was discharged home. Two weeks later however, the patient presented with slowing of speech, personality and behavioral changes and difficulty in resolving personal needs such as dressing. Neuropsychological assessment revealed deficits in attention, concentration, executive function, recall memory, organization and coordination and slurred speech. Cranial MRI revealed marked symmetrical hyperintense lesions involving bilateral lentiform and caudate nuclei. Skin prick tests to hymenoptera species were negative. Specific IgE levels were also undetectable. The patient's baseline tryptase level was 49 ng/mL (normal <14.1 ng/ml). Bone marrow biopsy showed dense compact mast cell aggregates in CD117 (c-kit) and tryptase stained sections. Co-expression of CD25 and CD2 were identified on mast cells by flow cytometry. An activating somatic codon Asp816→Val KIT mutation was detected in mast cells but not in neutrophils. Based on these findings, diagnosis of systemic mastocytosis was made. This patient represents the first case in English literature who was diagnosed with sytemic mastocytosis and frontal lobe syndrome. Frontal lobe dysfunction may emerge with bilateral basal ganglia lesions. Mast cell degranulation has been documented to enhance vascular permeability and to regulate blood-brain barrier permeability. Besides probable hypoxic encephalopathy, the increased tendency for mast cells to undergo spontaneous degranulation can be explanatory for vasogenic edema in systemic mastocytosis.

Key words: Bee sting, bee venom allergy, systemic mastocytosis, frontal lobe syndrome

Arı Sokmasına Bağlı Frontal Lob Sendromu

Özet

34 yaşında bir erkek arıcı, bal arısı ile sokulduktan 5 dakika sonra yüz ve boyun bölgesinde kızarıklık, nefes darlığı geliştiriyor ve bilincini kaybediyor. Acil serviste yapılan

muayenesinde hipotansiyon ve filiform nabız saptanıyor. 24 saat süren bilinçsizlik döneminin ardından olgu kendine geliyor ve taburcu ediliyor. İzleyen günlerde konuşmada yavaşlama, kişilik ve davranış değişiklikleri ve kişisel ihtiyaçlarını gidermede zorluk (örneğin giyinme) olduğu farkediliyor. Nöropsikolojik değerlendirmede dikkat ve konsantrasyon, yürütücü işlevler, organizasyon ve koordinasyon becerilerinde bozukluk yanında konuşma güçlüğü saptanıyor. Kraniyal MRG'de bilateral lentiform ve kaudat nukleuslarda simetrik hiperintens lezyonlar belirleniyor. Arı türleri ile deri prik testi ve spesifik IgE analizi negatif bulunuyor. Bazal triptaz düzeyi 49 ng/mL (normali <14.1) olarak saptanıyor. Kemik iliği biyopsisinde CD117 (c-kit) ve triptaz pozitif mast hücrelerinin sayıca artmış olduğu ve agregatlar oluşturduğu belirleniyor. Flow sitometrik incelemede mast hücrelerinde CD25 ve CD2 eksprese olduğu bulunuyor. Mast hücrelerinde Asp816→Val KIT somatik kodon mutasyonu saptanıyor. Bu bulgulara dayanılarak hastaya sistemik mastositoz tanısı konulmuştur. Olgumuz literatürde frontal lob sendromu bulguları oluşturan ilk sistemik mastositoz olgusudur. Frontal lob disfonksiyonu bilateral bazal ganglia lezyonları nedeni ile oluşmuş olabilir. Mast hücre degranülasyonu ile vasküler permeabilitenin arttığı ve mast hücrelerinin kan-beyin bariyeri permeabilitesini düzenlediği önceki çalışmalarda rapor edilmiştir. Olası hipoksik ensefalopati yanında, sistemik mastositoz olgularında mast hücrelerinin spontan degranülasyon eğilimlerinin artmış olması olgumuzda oluşan vazojenik ödemi açıklayabilir.

Anahtar Kelimeler: Arı sokması, arı venomu alerjisi, sistemik mastositoz, frontal lob sendromu

INTRODUCTION

Neurologic complications are rare in bee sting. Different inflammatory and vascular complications have been reported.[2,6,22,24] Frontal lobe dysfunction following a bee sting in association with basal ganglia lesions has not been previously described. In this report, we describe a case that was diagnosed as sytemic mastocytosis and frontal lobe syndrome due to bee sting. We also present a detailed diagnostic approach and discuss the probable pathogenetic mechanisms involved in basal ganglia lesions and frontal syndrome in our case.

CASE PRESENTATION

A 34 year-old beekeeper experienced flushing, breathing difficulty and loss of consciousness, five minutes after he got stung by a honeybee. He was admitted to a local emergency room with a blood pressure of 54/32 mmHg and a phyliform pulse of 120 beats/min. He was unresponsive to verbal stimulus, but spontaneous limb movements were present. The patient's medical history obtained from a family member revealed a similar episode of hypotension and syncope after he had been stung by a yellow jacket two years earlier. He received intravenous epinephrine and normal saline.

In an adult with symptoms of dyspnea and reduced blood pressure after exposure to a known allergen, the diagnosis of anaphylaxis is rather likely. Although skin and/or mucosal tissue involvement is more common than respiratory and cardiovascular symptoms in anaphylaxis, both skin or mucosal reactions might be absent in patients with insect sting allergy. Acute attacks of C1 esterase inhibitor deficiency, carcinoid syndromes and pheochromocytoma can all be associated with syncope, without urticaria. However, temporal relationship between symptoms and hymenoptera exposure could not be readily explained by these diagnoses. An elevated serum tryptase level could be helpful in confirming the diagnosis, provided that the serum or the plasma samples had been taken up to 4 hours after

the onset of symptoms. Insect sting allergy is the most likely diagnosis in this case. Thus, one should obtain skin testing with both honeybee and yellow jacket venoms and measure venom-specific IgE antibody concentrations.

After a period of unresponsiveness which lasted for about 24 hours, the patient gained conciousness and was discharged home. Two weeks later however, the patient presented with slowing of speech, personality and behavioral changes, and difficulty in resolving personal needs such as dressing. Neuropsychological assessment revealed deficits in attention, concentration, executive function and recall memory, disorder of planning, organization and coordination, and slurred speech. Neurological and physical examination was otherwise normal.

Diffuse bilateral cerebral or brain stem involvement is unlikely in this patient because of the absence of abnormal findings on neurologic examination. The neuropsychological and behavioral profile of the patient leads us on to frontal lobe localization. Attention and concentration deficit, disorder of planning, organization and coordination, and executive dysfunction along with the behavioral changes mentioned above are all consistent with dorsolateral frontal involvement. Memory deficit suggests basal forebrain damage, while dysfluent speech is compatible with a frontal operculum injury. Loss of insight, irritability, inappropriateness, impulsivity and poor judgment are characteristics of an orbitofrontal lobe lesion. These findings suggest a fully developed frontal syndrome.

EEG and a cranial MRI could assist in the differential diagnosis of encephalopathy. The resting awake EEG of the patient showed background alpha activity at 8-9 Hz in parieto-occipital regions with rare theta rhythms of 6-7 Hz. On cranial MRI, FLAIR and T2-weighted images revealed marked symmetrical hyperintense lesions involving bilateral lentiform and caudate nuclei. Diffusion-weighted sequences also showed bilateral symmetrical high-intensity areas in the regions of caudate and lentiform nuclei. ADC values were increased in these areas (Figures 1,2,3). Contrast-enhanced T1-weighted images demonstrated peripheral enhancement of bilateral caudate nuclei. Intracranial MR arteriography and venography were both normal.

Discrimination between different types of brain edema with MRI is extremely important in terms of diagnosis, treatment planning and prognostication of patients. Cytotoxic brain edema, once started, is irreversible and ultimately leads to cell death. Hence, cytotoxic edema is a bad prognostic sign with regard to mortality, morbidity and response to treatment, whereas vasogenic brain edema indicates that cerebral damage is usually reversible and a favorable response to treatment is likely. As in the case of ischemia and infarction, cytotoxic edema is hyperintense on DW images and associated with decreased ADC values. On the other hand, vasogenic edema as seen in cerebral infection, primary or metastatic mass lesion, metabolic encephalopathy, and posterior reversible encephalopathy syndrome has a hyperintense appearance on DW images combined with increased ADC values. The MRI characteristics of our patient suggests vasogenic edema. The patient's history, sudden onset of clinical symptoms following an allergen exposure and bilateral symmetrical vasogenic edema on MRI, excluding an infection and a tumoral lesion, would be compatible with a reversible encephalopathy syndrome.

Encephalopathy is a diagnosis of exclusion. Metabolic etiologies include disorders of renal and hepatic function, impaired glucose metabolism, hypercalcemia and other electrolyte imbalances and acid-base disorders. Blood glucose, renal and liver function tests, electrolytes, calcium and arterial blood gas

values were within normal limits in our patient. Complete blood count, erythrocyte sedimentation rate, and coagulation studies were also normal. Protein C, protein S, antithrombin III, copper, ceruloplasmin, lactate, pyruvate, vitamin B12, and folate levels, protein and immunofixation electrophoresis, thyroid function tests, anti-TPO and anti-M antibody levels, parasitological tests, autoimmune and vasculitic markers, full body CT scan, and urinalysis were all normal. The cerebrospinal fluid (CSF) was also examined. CSF was clear in appearance, with a normal pressure, cell count and glucose and protein levels. Blood and CSF cultures and serological studies were negative for infectious etiologies.

Neurological complications following bee sting are rare. However, because of all laboratory tests were negative for other possible etiologies, bee-sting related encephalopathy is highly likely in this patient.

Skin prick tests to Apis mellifera, Vespa crabro, Polistes dominulus, Vespula species and Bombus terrestris were performed[19], and were negative with 10 µg/ml, 100 µg/ml, 300 µg/ml concentrations (ALK, Abello, Madrid, Spain). Specific IgE levels were also undetectable (Pharmacia UniCAP, Uppsala, Sweden).

The patient had a negative skin prick test and no specific IgE antibodies to insect venoms. Skin prick test is more sensitive than the serum-specific IgE test in the diagnosis of hymenoptera venom allergy. Therefore, one would repeat the skin prick test. In case of a second negative skin prick test, one would then perform an intradermal test which is more sensitive but associated with a higher risk of systemic reactions. Nevertheless, negative allergy tests results do not rule out an anaphylactic reaction to bee sting, because non-IgE related mechanisms may be involved. In addition, negative allergy tests in subjects with severe anaphylaxis after wasp or bee sting can be a sign of unrecognized mastocytosis. One would then measure the baseline tryptase concentration.

Intradermal tests were performed at 0.001, 0.01, 0.1, 1 µg/ml concentrations. At 1 µg/ml concentration, Apis mellifera and Vespula species yielded positive responses. The tryptase level was 49 ng/mL (N<14.1 ng/ml). At four months following the anaphylactic reaction, the neuropsychological examination had returned to normal. Bilateral lentiform hyperintensities of vasogenic edema had totally regressed on MRI. Bilateral caudate hyperintense lesions had decreased by about 60% in size.

Baseline tryptase levels are typically elevated in systemic mastocytosis, however they may also be elevated in cutaneous mastocytosis, end-stage renal disease, myeloid neoplasms, refractory anemia, and hypereosinophilic syndrome. All except the first are unlikely, given the normal results of renal function tests, hemogram and erythrocyte sedimentation rate. One would want to know whether he has the classical skin lesions of urticaria pigmentosa characterized with fixed, reddish brown maculopapular exanthema, solitary mastocytoma or diffuse cutaneous mastocytosis.

On physical examination, the patient had no suspicious lesions for cutaneous involvement of mastocytosis, no Darier's sign or organomegaly. In addition, there was no history of pruritis, flushing, or blistering.

Cutaneous involvement is a common manifestation of systemic mastocytosis. Although clinical evidence of cutaneous mastocytosis was absent in our patient, the elevated baseline tryptase level is worrisome and makes us wonder whether systemic mastocytosis is present. The patient does not have skin or gastrointestinal symptoms such as flushing, pruritis, diarrhea or abdominal cramping to suggest the presence of systemic

mastocytosis. Nevertheless, systemic mastocytosis without skin involvement was recognized as a clinical entity and later found to be associated with anaphylaxis due to hymenoptera sting. In addition, an underlying mastocytosis should be suspected in patients with anaphylaxis associated with cardiovascular symptoms in the absence of urticaria or angioedema. Therefore, we would perform a bone marrow (BM) aspiration and biopsy to search for the possibilty of an underlying systemic mastocytosis.

A BM aspiration and biopsy was performed. Mast cells with abnormal morphology were found in BM smears (Figure 4) and dense compact BM mast cell (MC) aggregates were detected in CD117 (c-kit) and tryptase stained BM sections (Figure 5A and 5B). In addition, CD25 and CD2-positive MC were identified by multiparametric flow cytometry analysis. Because these findings suggested mastocytosis, a DNA sequencing analysis was performed to look for KIT mutations. Genomic DNA from FACS-purified populations of BM MC and neutrophils was used.[10] A somatic activating codon Asp816→Val KIT mutation was detected in MC but not in neutrophils.

Multifocal dense infiltrates of CD25-positive mast cells in the bone marrow along with an elevated baseline tryptase level and the KIT Asp816Val mutation confirms the diagnosis of systemic mastocytosis.

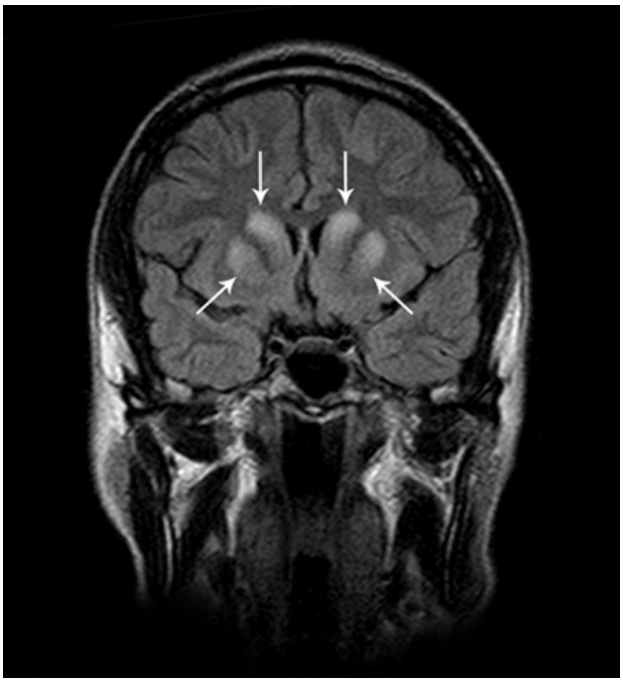

Figure 1: *Coronal FLAIR MR image shows hyperintense signals involving caudate and lentiform nuclei bilaterally.*

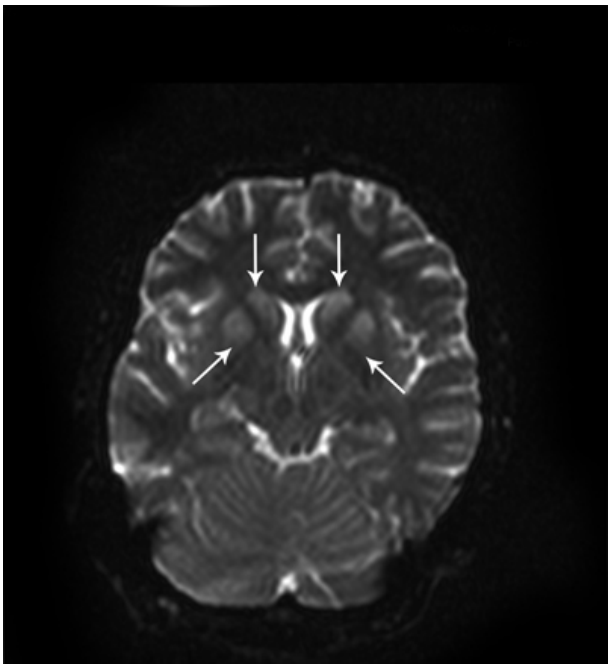

Figure 2: *Axial diffusion-weighted MR image showing bilateral high signal intensity in caudate and lentiform nuclei.*

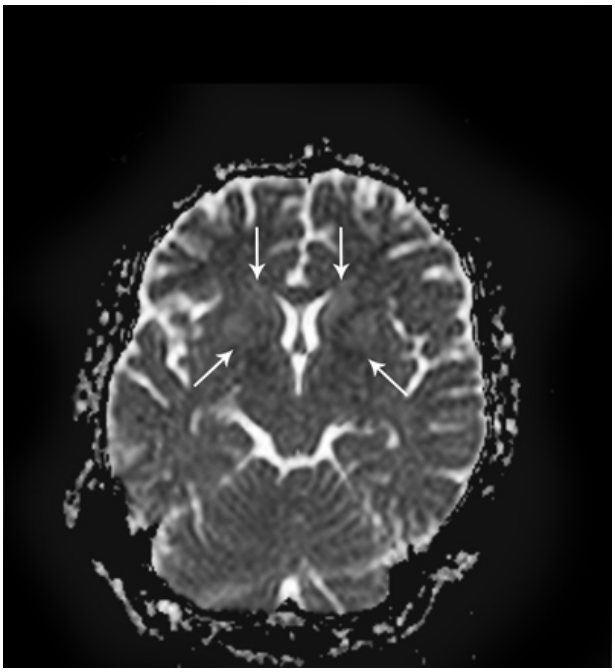

Figure 3: *Axial ADC map shows bilateral caudate and lentiform hyperintensities corresponding to vasogenic edema.*

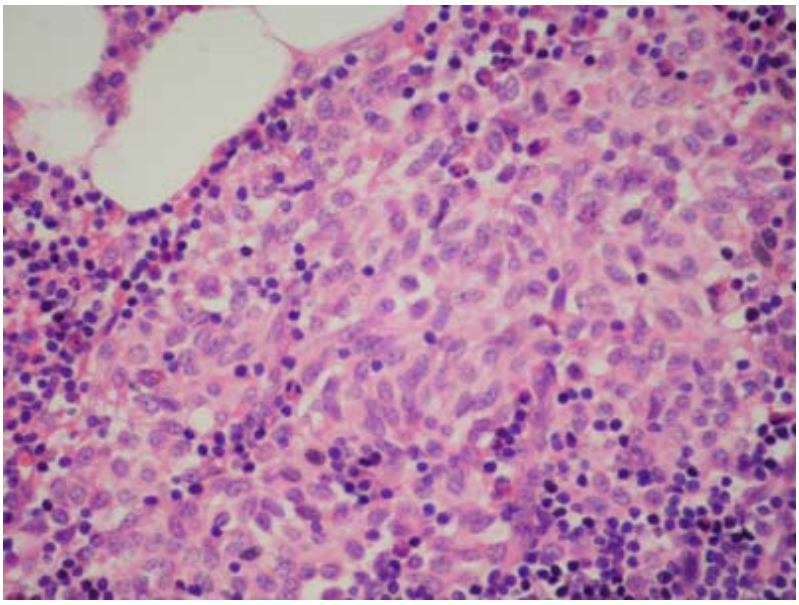

Figure 4: *Bone marrow biopsy revealed focal lesions of mast cells some of which were in spindled shape, admixed with lymphocytes and reactive eosinophils (Hematoxylin & Eosin, x40).*

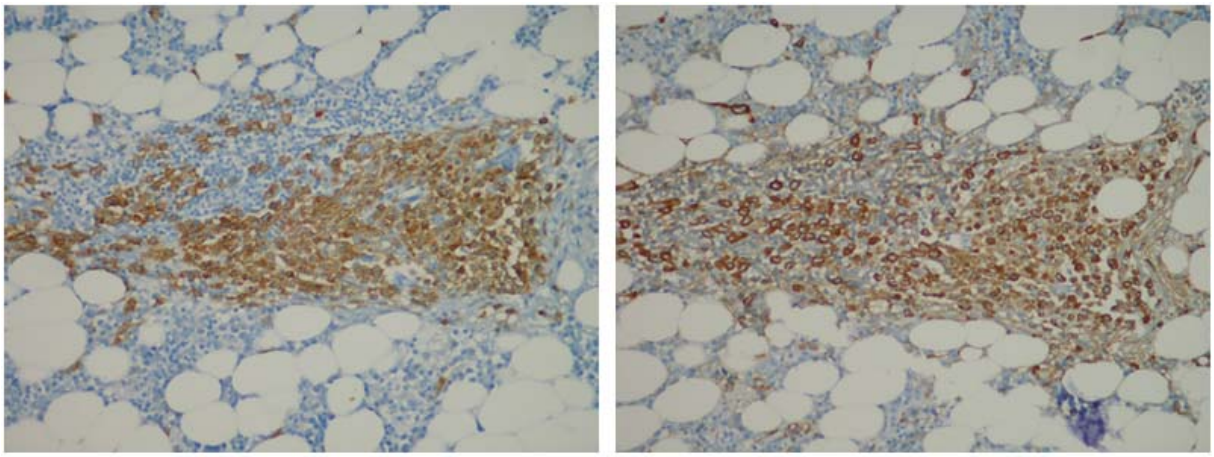

Figure 5A and 5B: *Immunohistochemical staining for CD117 (A, x20) and for mast cell tryptase (B, x20) showed strong positivity, confirming mast cell origin of the aggragates.*

DISCUSSION

The prevalence of systemic mastocytosis is not exactly known, but it may be as high as 6% in patients who have experienced anaphylaxis following hymenoptera sting.[4] Anaphylaxis is more common in patients with systemic mastocytosis[7] when compared with the normal population.[11] Moreover, anaphylaxis symptoms differ in patients with systemic mastocytosis from those without systemic mastocytosis. In general, urticaria and angioedema are the most common symptoms of anaphylaxis reported in more than 85% of nonmastocytosis cases.[25] However, in one study, urticaria and angioedema were observed in less than

10% of mastocytosis patients.[7] Therefore, in the absence of urticaria and angioedema, mast cell disease should be considered in patients with anaphylaxis.[4] Of all anaphylactic reactions in systemic mastocytosis, 60% were classified as severe and 43% were associated with shock and unconsciousness. In patients with mastocyctosis, cardiovascular symptoms including dizziness, presyncope, tachycardia, hypotension and shock were very common.[7] In contrast, only one third of the patients without mastocyctosis experienced syncope or dizziness. The most common elicitor for anaphylaxis in adults with mastocytosis is hymenoptera sting, whereas in patients without mastocytosis, food and medication are most commonly implicated.[3,7,25]

Current classification of mastocyctosis is based on the revised 2008 WHO consensus criteria which groups cases into two main categories as cutaneous mastocytosis (CM) and systemic mastocytosis (SM). In CM, MC accumulations are typically limited to the skin; but in SM, MCs are also detected in extracutaneous organs especially in the BM as multifocal dense infiltrates. SM is further divided into following categories: indolent systemic mastocytosis (ISM), SM with an associaed clonal hematologic non-mast cell lineage disease (AHNMD), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL). Indolent systemic mastocytosis (ISM) is the most common subtype with an excellent prognosis. Smoldering SM, a subvariant of ISM, is characterized by the presence of at least two of 'B findings' which include dysmyelopoiesis without cytopenia, organomegaly without functional impairment (hepatomegaly, splenomegaly, lymphadenopathy) and a massive MC burden (>30% MC infiltration in bone marrow and/or tryptase>200 ng/ml) and carries a significantly inferior survival as compared with the other ISM.[13,21] ASM is characterized by impaired organ-function, also known as a 'C-finding', due to infiltration of the bone marrow, liver, spleen, gastrointestinal tract, or skeletal system by pathologic MCs. In our case, absence of B- and C-findings was consistent with ISM. Normal bone marrow and peripheral blood examinations exclude MCL and AHNMD. Typical skin lesions of urticaria pigmentosa are present in approximately 80% of patients with SM. On the other hand, ISM in the absence of skin involvement (ISMs-) has been recognized as an entity since 1991 as in our patient.[18]

Evidence suggests that systemic mastocytosis is a clonal disorder with increased mast cell proliferation. The strongest evidence for clonality comes from studies that have shown activating mutations in c-kit, the receptor for the stem cell factor (SCF). SCF is essential for differentiation and maturation of mast cells from hematopoietic progenitors. Unlike other hematopoietic cells which loose c-kit expression during the developmental program, mast cells retain receptor activity throughout their life span. The activating c-kit mutations have been described in >90% of patients. The most common mutation occurs at codon 816 substituting valine for aspartate (Asp816Val). Other uncommon somatic and germ-line mutations have also been reported. Although the precise mechanisms by which the c-kit mutations result in mastocytosis remains unknown, preclinical evidence suggests that chronic SCF independent activation of the PI3K-akt pathway is essential.[10,12]

The pathogenetic relevance of the different KIT mutations in SM is still not fully understood. In most cases with poor prognosis SM, as well as in a smaller proportion of ISM, involvement of the $CD34^{+}$ hematopoietic progenitors and other hematopoietic cell compartments by the KIT-mutated clone was detected, supporting the origin of SM in a pluripotent hematopoietic stem cell.[10] In one study of ISM, presence of the KIT mutation in all hematopoietic lineages was

a predictor for disease progression to more aggressive subtypes.[9]

Reduced and even absent venom specific serum IgE levels are commonly seen in patients with mastocytosis allergic to hymenoptera venom, as a result of increased absorption of circulating IgE by abundant tissue mast cells.[16] This, might lead to delayed venom immunotherapy, a potentially a life-saving treatment in mastocytosis which should be recommended for life-long.[20]

Neurologic complications are rare in bee sting. Hemorrhage, infarction, encephalitis, acute disseminated encephalomyelitis (ADEM) and hypoxic encephalopathy have all been reported.[2,6,22,24] We excluded these pathologies in our patient except hypoxic encephalopathy on the basis of clinical presentation, laboratory tests and radiological imaging. The neuropsychological findings in our patient were consistent with extensive frontal lobe involvement, but surprisingly, only bilateral symmetrical basal ganglia lesions were found.

When basal ganglia involvement is present in isolation, discrimination between different cerebral edema types can be difficult. Diffusion imaging and ADC mapping could be used to differentiate reversible encephalopathy, which demonstrates increased ADC values caused by vasogenic edema, from cytotoxic edema which show decreased ADC values.[15] However, cytotoxic and vasogenic edema can occur together in hypoxic encephalopathy.[1,15] Pathologically, vasogenic edema follows cytotoxic edema in later periods.[1] Accordingly, MR imaging studies of brain can demonstrate both cytotoxic and vasogenic edema.[15]

On the other hand, hypoxic injury primarily affects the gray matter structures of brain and damage to basal ganglia is one of the main hypoxic injury sites.[14] Our patient was unconscious and hypotensive immediately after the bee sting. A hypoxic injury was likely in our case, based on reasoning from pathological and radiological experiences mentioned above. Additionally, degranulation of mast cells and bioactive mediators targeting vascular basal lamina in addition to acute hypoperfusion and localized brain hypoxia could be involved in vasogenic edema in the presented case.[17,23]

Frontal lobe dysfunction following a bee sting in association with basal ganglia lesions has not been previously described. Frontal-like syndrome may emerge with bilateral basal ganglia lesions as in our case, and this interesting phenomenon could be explained by disconnection of frontal-subcortical circuits. All frontal-subcortical circuits share same anatomical structures. Striatum and globus pallidus are located centrally in these circuits.[5,8] Therefore, involvement of these basal ganglia nuclei is probably explanatory for extensive frontal dysfunction in our case, which exhibits all of dorsolateral, orbitofrontal and anterior cingulate neuropsychological findings.

Acknowledgement

Written consent was obtained from the patient for publication in a web-based journal.

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Received by: 18 May 2013
Revised by: 22 May 2014
Accepted: 25 May 2014

The Online Journal of Neurological Sciences (Turkish) 1984-2014
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

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