GENERALIZED TELANGIECTASIA MACULARIS ERUPTIVA PERSTANS ASSOCIATED WITH SKELETAL ABNORMALITIES: EVALUATION OF A PROBABLE SYSTEMIC INVOLVEMENT BY BLOOD FLOW CYTOMETRY, TRYPTASE AND C-KIT MUTATION ANALYSIS

Betül Taş,[1] Saadet Pilten,[2] Deniz Ekinci,[3] Ramazan Albayrak,[3] Mehmet Sar[4]

[1] Bağcılar Eğitim ve Araştırma Hastanesi, Dermatoloji Kliniği, İstanbul
[2] Bağcılar Eğitim ve Araştırma Hastanesi, Biyokimya Laboratuvarı, İstanbul
[3] Bağcılar Eğitim ve Araştırma Hastanesi, Radyodiagnostik Kliniği, İstanbul
[4] Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, Patoloji Laboratuvarı, İstanbul

ABSTRACT

Telangiectasia macularis eruptiva perstans (TMEP) is an uncommon form of cutaneous mastocytosis (CM). We report an 19-year-old girl with generalized TMEP in the article. The patient also had accompanying congenital skeletal abnormalities. The histopathological examination of the cutaneous lesions showed scattered mast cells that were positively stained with toluidin blue, CD25 and CD117. Because of skin lesions spreading and accompanying skeletal abnormalities, we performed a D816V mutation analysis of the c-kit gene, a tryptase enzyme analysis and flow cytometric analysis of CD2, CD4, CD25, CD34 and CD117 in the peripheral blood in order to investigate a probable systemic involvement. As a result of these tests no evidence to support a systemic involvement was found. To the best of our knowledge, our patient was the first TMEP case to have both the congenital skeletal abnormalities and the generalized skin lesions. In this report we also aimed to draw attention to usefullness and significance of these noninvasive tests in the evaluation of systemic involvement in patients who have generalized TMEP, especially in the case of an absence of prominent aggregates of mast cells in the skin, and in the cases where it is not possible to perform a bone-marrow biopsy.

Key Words: *Mastocytosis, cutaneous, c-kit mutation, tryptase, blood flow cytometry.* ***Nobel Med 2014; 10(2): 92-95***

İSKELET ANOMALİLERİNİN EŞLİK ETTİĞİ JENERALİZE TELENJİEKTAZYA MAKÜLARİS ERÜPTİVA PERSTANS: KAN AKIM SİTOMETRİSİ, TRİPTAZ VE C-KİT MUTASYON ANALİZİYLE OLASI SİSTEMİK TUTULUMUN DEĞERLENDİRİLMESİ

ÖZET

Telenjiektazya makülaris erüptiva perstans (TMEP) kütanöz mastositozların en nadir tipidir. Bu makalede jeneralize TMEP'li 19 yaşındaki bir kız olgu sunulmaktadır. Hastanın aynı zamanda hastalığına eşlik eden konjenital iskelet anomalileri de mevcuttu. Deri lezyonlarının histopatolojik tetkikinde toluidin mavisi, CD25 ve CD117 immünohistokimyaları ile pozitif boyanan dağınık sayıda mast hücre infiltrasyonu izlendi. Olgunun deri lezyonlarının yaygınlığı ve eşlik eden konjenital anomalileri nedeniyle, olası bir sistemik tutulumun tetkiki amacıyla; kan triptaz düzeyi, kan akım sitometrisiyle CD2, CD4, CD25, CD34 ve CD117 mast hücre immün fenotiplerinin analizi ve c-kit gen D816V mutasyonu araştırıldı. Testler sonucunda sistemik tutulumu destekleyecek herhangi bir bulgu saptanmadı. Bildiğimiz kadarıyla olgumuz, bu kadar yaygın deri lezyonları ve konjenital iskelet anomalilerinin birlikte görüldüğü literatürdeki ilk TMEP olgusudur. Makalemizde ayrıca, özellikle deride belirgin mast hücre infiltrasyonunun bulunmadığı ve kemik iliği biyopsisi yapmanın mümkün olmadığı durumlarda, bu noninvaziv testlerin, jeneralize TMEP olgularının sistemik tutulumunun değerlendirilmesindeki kullanışlılığı ve önemine değinilmiştir.

Anahtar Kelimeler: Mastositoz, cutaneous, c-kit mutasyonu, triptaz, kan akım sitometrisi. **Nobel Med 2014; 10(2): 92-95**

INTRODUCTION

Mastocytosis is a disease characterized by the accumulation of mast cells in various organs, especially in the skin.[1,2] According to the *2008* World Health Organization (WHO) ***Classification of Tumours of Haematopoietic and Lymphoid Tissues*** six categories of mastocytosis have been defined: extracutaneous mastocytoma, indolent systemic mastocytosis, systemic mastocytosis associated with other clonal hematological non-mast cell lineage disease, aggressive systemic mastocytosis, mast cell leukemia and mast cell sarcoma.[2] In the classification, in addition to a major conventional histopathological criterion (multifocal dense aggregates of ≥15 mast cells in bone marrow and/or other extracutaneous tissues), four minor morphological (atypical mast cells in smears or biopsy sections of bone marrow or other extracutaneous organs), immunophenotypical (CD25+ and/or CD2+ mast cells), molecular (D816V KIT mutation) and biochemical (serum tryptase levels persistently >20 ng/ml) criteria are proposed for the diagnosis of systemic mastocytosis.[3] On the other hand, cutaneous mastocytosis (CM) can be classified as follows; nodular, diffuse (erythrodermic), maculopapular, urticaria pigmentosa and Telangiectasia macularis eruptiva perstans (TMEP).[1] TMEP is an uncommon form of CM and it occurs primarily in adults.[4] The systemic involvement of the unique mast cell disease is rare.[1,5]

CASE

A nineteen-year-old girl was presented to our outpatient clinic with a thirteen-year history of blemishes that were seen throughout the whole body. The lesions started on her left leg when she was 6 years old, and, began to be seen on her trunk, neck and face over the course of the years. The lesions were symptomless and the patient had not received any treatment. The patient complained of poor image of the lesions. She had no family history of skin disease. The dermatological examination showed extensive, light to dark-brown, slightly-depressed, 4-5 mm in size, maculopapular eruption on the trunk, neck, face and legs (Figure 1a, b, c, d, e, f). The lesions predominantly were on the left side of the body and most of them localized according to the lines of Blaschko. When a brown macule was rubbed on the leg, it did not demonstrate a wheal. With the dermoscopy, multiple fine telangiectatic vessels arranged in a reticular pigment network were seen. Review of the systems was negative for flushing, asthma, dizziness, diarrhea and syncope. In the orthopedic examination, a congenital anonichia of the third toe, congenital simple pedal syndactily, interdigital web between the second and third toe on the left foot (Figure 1g), right acetabular displasia and a mild "right pelvic tilt" were detected. Additionally, in the examination of the oral cavity, orthodontic tooth alignment abnormalities and congenital hypoplasia of the maxilla were detected (Figure 1h). Regional or systemic palpable lymphadenomegaly and hepatosplenomegaly were not present. The rest of the systemic examination was normal.

A complete blood count, peripheral blood smear, erythrocyte sedimentation rate, rapid plasma reagin and comprehensive biochemical examination that included the level of the total immunoglobuline E, thyroid parameters and cancer markers were normal. The serum tryptase level was normal at 2.3 pg/L (reference range <11.4 pg/L). Due to the spreading of the lesions, a systemic mast cell disease was investigated. In order to detect it, a c-kit proto-oncogene (D816V) mutation analysis and flow cytometric analysis of CD2, CD4, CD25, CD34, CD117 in the peripheral blood were examined. The D816V-mutation of the c-kit- receptor-gene in the exon 17 was analyzed on genomic DNA by direct sequencing of the amplified PCR products in both directions, using the dye-deoxy terminator method (Synlab Medizinisches Versorgungszentrum, Leinfelden, GmBH, Germany). No mutation in D816V was detected, and the above-mentioned markers of mast cells were within the normal limits as 89.6%, 12.5%, 41.2%, 1.5% and 0.8%, respectively (Figure 2). The abdominal ultrasonography showed no additional pathology. In the spine, pelvis, chest, and left foot radiographs and panoramic dental graphy to examine additional pathology, a simple pedal digital syndactily, right acetabular displasia, mild right pelvic tilt and maxillar hypoplasia were confirmed.

The excisional biopsy of the skin lesions showed an epidermal achantosis, increased pigmentation of the basal layer, scattered accumulations of mast cells mixed with increased dermal melanophages and mononuclear lymphocytic infiltrate around the prominent capillaries in the upper dermis (Figure 3a). These mast cells were stained positively with toluidine blue (Figure 3b). Immunohistochemical assessment of the mast cells for CD25 and c-kit (CD117) was positive (Figure 3c, d). Unfortunately, a bone-marrow biopsy could not be performed because the patient did not give consent. The suggested clinical and dermoscopic picture and the typical histopathology confirmed the diagnosis of TMEP. For the treatment of the lesions, a pulsed-dye laser therapy was planned.

DISCUSSION

TMEP is a rare form of cutaneous mastocytosis described by Parkes Weber in 1930.[5,6] Although there have been some case reports of TMEP in children, the disease usually affects young adults.[5-7] The age of the patients has an important value for prognosis. Fifty percent of the pediatric patients show resolution of the symptoms in adolescence and only 10 to 15 percent of →

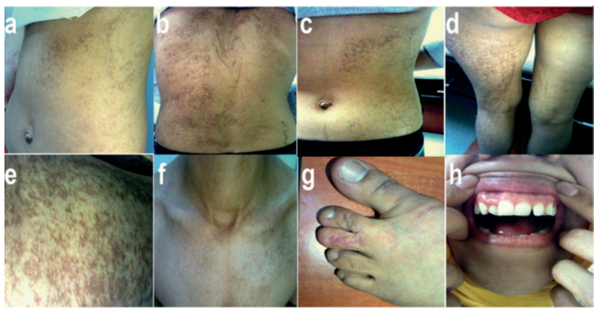

Figure 1: Clinical appearances of the generalized skin lesions (a, b, c, d, e, f), congenital anonichia of the third toe, simple pedal syndactily and interdigital web (g) and the tooth alignment abnormalities in the maxilla (h).

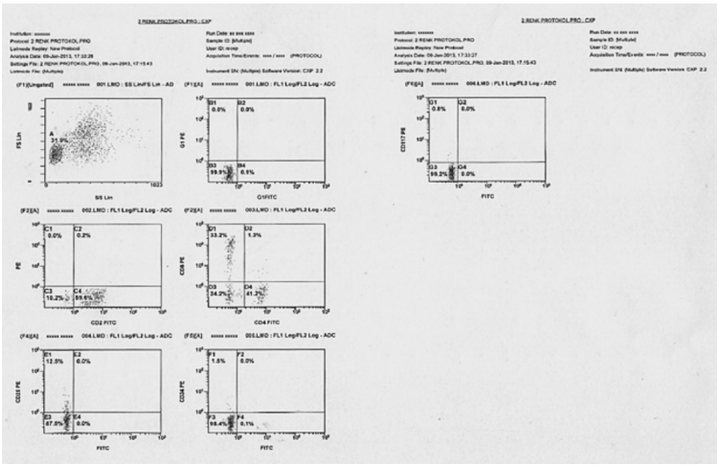

Figure 2: Results of the flow cytometric analysis of the mast cell markers in the peripheral blood.

them continue into adulthood.[5] The lesions of our patient have been seen on the left leg since the age of 6. Familial cases have been reported rarely in literature.[6] Our patient was a sporadic case. TMEP is usually present as diffuse, confluent, indistinct-bordered, telangiectatic and hyperpigmented, reddish-brown macules on especially the trunk and extremities.[5,7-9] The face involvement may occur. Sometimes they may follow the lines of Blaschko. The lesions do not characteristically display Darier's sign of urtication when rubbed.[9] In the dermoscopy of the patients of TMEP, classically a brown-reticular lines occur. Akay et al. have additionally reported on a characteristic vascular reticular pattern in addition to the classical findings in the case of TMEP.[1] Our clinical findings were consistent with the literature. Furthermore, we detected both a pigment network and vascular lines on the dermoscopy. Although TMEP has been thought to be a form of mastocytosis limited to the skin, the signs of a systemic involvement such as dizziness, dyspnea, syncope, headache, flushing, diarrhea, splenomegaly, abnormal skeletal radiographs, and bone marrow involvement can be found.[6,9] Additionally, some hematological abnormalities may also be present. Rarely, the association with multiple myeloma and polycythemia vera has been reported.[5] We did not detect any systemic findings. Since there was no pathological image of the bone, we thought that the skeletal abnormalities were just accompanying the findings. Moreover, it is believed that a transitory deregulation of growth factors occurs in children with TMEP.[5] The skeletal birth abnormalities in our patient such as congenital anonichia, pedal syndactily, pedal interdigital web, maxillar hypoplasia and right pelvic tilt have not been reported previously in the cases of TMEP. We thought that the abnormalities in our patient could have been due to the deregulation of some growth factors in the post-zygotic autosomal somatic division period.

On the other hand, the development, proliferation, maturation, and migration of mast cells are regulated by stem cell factor (SCF)/ kit signaling.[9] The c-kit proto-oncogene encodes the kit, a tyrosine kinase, which is the receptor of mast-cell growth factor. A somatic c-kit mutation in codon 816 led to spontaneous activation of the mast-cell growth-factor receptor and mast-cell hyperplasia.[6] It is thought that the c-kit mutations may indicate a more aggressive course of the mastocytosis.[5] In addition to the c-kit mutation, high tryptase serum levels may show a systemic involvement in the mastocytosis.[5,6,9,10] Torrelo et al. have reported that serum tryptase is the best marker for mast cell burden in children, and, at baseline, correlates well with the severity of symptoms in childhood mastocytosis. Systemic mastocytosis definitely may occur in children, but bone marrow studies to demonstrate a systemic involvement are not routinely performed nor they are recommended. It can be estimated that around 30% of children may have bone-marrow involvement as demonstrated by showing aggregates of mast cells or by flow cytometry of mast cells expressing the aberrant CD25 marker.[11] In recent years, flow cytometric immunophenotyping of mast cells has become a useful test in the evaluation of systemic mastocytosis, with the current criteria of positivity based on aberrant expression of CD2 and/or CD25 by the mast cells. On the other hand, Pozdnyakova et al. have reported a discrete presence of CD117-positive mast cells on flow cytometric analysis of bone-marrow which is an indicator of the presence of a mast cell neoplasm and may be a useful new diagnostic criterion for systemic mastocytosis, even in the absence of an aberrant mast cell immunophenotype.[2]

Cutaneous findings of the patient have begun at the age of 6 and she did not have any systemic symptoms up to now. We did not find any abnormalities in the routine laboratory tests. However, due to the extensive skin lesions and additional congenital defects, we conducted serum tryptase level, c-kit (D816V) mutation analysis, and flow cytometric analysis of the mast cell markers such as CD2, CD4, CD25, CD34 and CD117 in the peripheral blood in order to investigate a probable systemic involvement. Since the patient did not give a consent for a bone-marrow biopsy, we could not do neither an histopathological examination nor a flow →

cytometric analysis in the bone marrow. Even though we did not perform these examinations, actually, the rest of the findings of our patient did not exactly fill the previously mentioned criteria which were necessary for the diagnosis of a systemic mastocytosis. As a result of performed tests, because all of the indicators were normal or negative, absence of intense skin infitration of mast cells, early onset of the disease, and the fact that the patient had no systemic symptoms up to now we thought that there was no need for a bone-marrow examination in order to show a systemic involvement.

Histologically, TMEP is known for scattered mast cells lined up around the dilated capillaries and venules of the superficial vascular plexus. In some cases, the number of mast cells falls within the range observed in normal skin and therefore cannot be detected by a routine histological examination.[12] We also found a scattered and slight increased number of mast cells around the dilated blood vessels in the papillary dermis and some increased pigmentation of the epidermal basal layer. Immunohistochemically, mast cells can be demostrated with Giemsa, toluidine blue chloroacetate esterase, aminocaproate esterase, Leder stain, CD25 and c-kit (CD117) staining.[1,2,5,7,9]

We also showed the scattered mast cells with CD25, c-kit and toluidine blue. In differential diagnosis, carcinoid syndrome 6 and other exanthematous skin diseases 1 should be considered. There is no gold standard medication for the treatment of TMEP. The treatment is symptomatic. For pruritus, urticaria and flushing, H1 antagonists can be used.[5,7] The patients should avoid factors that stimulate the mast cell's degradation such as high temperatures, alcohol, sun exposure and some drugs.[5] The other treatment modalities are PUVA, 585 nm flashlamp pumped dye laser, doxepin, cromolyn sodium, topical and systemic corticosteroids, leukotriene antagonists, alpha interferon, "electron beam" radiation, montelucast and topical pimecrolimus.[1,4,5]

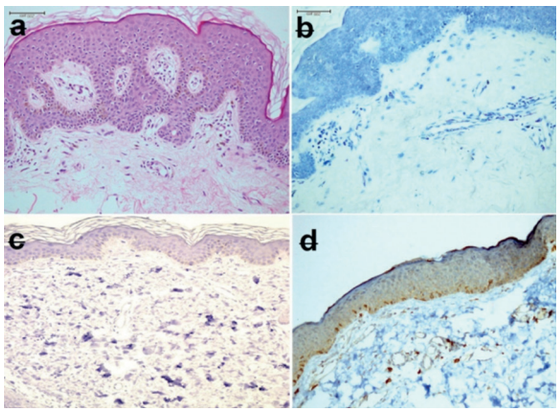

Figure 3: Histopathological appearance of the skin. **a)** HEx200 **b)** Toluidin bluex200 **c)** CD25x200 **d)** CD117x200

CONCLUSION

In conclusion, TMEP is an uncommon form of CM. Although TMEP is a cutaneous manifestation of mastocytosis, systemic involvement may occur. For the patients who have generalized skin lesions, or/and additional system abnormalities, detection of blood tryptase levels, immunophenotyping of mast cells with blood flow cytometry, and D816V exon 17 mutation analysis of the c-kit gene can be useful and noninvasive adjunctive tests in the evaluation of systemic involvement, especially in the case of an absence of prominent mast cells aggregates in the skin, and in cases where it is not possible to perform a bone marrow biopsy. To the best of our knowledge, the patient who presented is the first reported case in literature in terms of the coexistence of these congenital skeletal deformities and the disease.

* The authors declare that there are no conflicts of interest.

C **CORRESPONDING AUTHOR:** Betül Taş Atakoy 7-8. Kısım, Martı Sitesi, 14/105, Bakırkoy/Istanbul betulavc@yahoo.com

✔ **DELIVERING DATE:** 08 / 01 / 2014 • **ACCEPTED DATE:** 25 / 02 / 2014

REFERENCES

1. Akay BN, Kittler H, Sanli H, Harmankaya K, Anadolu R. Dermatoscopic findings of cutaneous mastocytosis. Dermatology 2009; 218: 226-230.
2. Pozdnyakova O, Kondtratiev S, Li B, Charest K, Dorfman DM. High-sensitivity flow cytometric analysis for the evaluation of systemic mastocytosis including the identification of a new flow cytometric criterion for bone marrow involvement. Am J Clin Pathol 2012; 138: 416-424.
3. Morgado JM, Sanchez-Munoz L, Teodosio CG, et al. Immunophenotyping in systemic mastocytosis diagnosis: 'CD25 positive' alone is more informative than the 'CD25 and/or CD2' WHO criterion. Mod Pathol 2012; 25: 516-525.
4. Lee HW, Jeong YI, Choi JC, et al. Two cases of telangiectasia macularis eruptiva perstans demonstrated by immunohistochemistry for c-kit (CD 117). J Dermatol 2005; 32: 817-820.
5. Costa DL, Moura HH, Rodrigues R, Pineiro-Maceira J, Ramos-E-Silva M. Telangiectasia macularis eruptiva perstans: a rare form of adult mastocytosis. J Clin Aesthet Dermatol 2011; 4: 52-54.
6. Nguyen NQ. Telangiectasia macularis eruptiva perstans. Dermatol Online J 2004; 10: 1.
7. Chung-Leddon J. Telangiectasia macularis eruptiva perstans. Dermatol Online J 2000; 6: 6.
8. Ragi J, Lazzara DR, Harvell JD, Milgraum SS. Telangiectasia macularis eruptiva perstans presenting as island sparing. J Clin Aesthet Dermatol 2013; 6: 41-42.
9. Noda S, Lee JB, Li K, Schwartz L. Unilateral telangiectasia macularis eruptiva perstans with a clear demarcation at the midline of the trunk. Eur J Dermatol 2012; 22: 407-408.
10. Altiner A, Tzu J, Patel R, Meehan S, Sanchez M. Telangiectasia macularis eruptiva perstans. Dermatol Online J 2011; 17: 7.
11. Torrelo A, Alvarez- Twose I, Escribano L. Childhood mastocytosis. Curr Opin Pediatr 2012; 24: 480-486.
12. Rishpon A, Matz H, Gat A, Brenner S. Telangiectasia macularis eruptiva perstans: unusual presentation and treatment. Skinmed 2006; 5: 300-302.