Is BCL11B a potential candidate gene for the diffuse cutaneous mastocytosis: A case report

BCL11B geni diffüz kutanöz mastositoz için potansiyel bir aday gen midir: Olgu sunumumu

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SUMMARY

Objective: Mastocytosis is a heterogeneous clinical phenotype spectrum characterized by the accumulation of mast cells in various organs. Cutaneous mastocytosis is the skin bounded form of this spectrum. Diffuse Cutaneous Mastocytosis (DCM) is a rare type of cutaneous mastocytosis that accounts for only 1 to 5% of all cases. The aim of this study is to report the molecular characterization of a Turkish patient with DCM with a large duplication on the long arm of chromosome 14, including the BCL11B (CTIP2) gene.

Case: A 32-months-old girl was referred to our department because of DCM and stuttering. In our patient who was born at 38 weeks of gestation after an uneventful pregnancy, in the neonatal period; recurrent episodes of diarrhea and atopic dermatitis began and DCM was diagnosed due to diffuse bullous lesions on the skin at the age of 4 months. Although growth and motor development were normal, there was language delay. Routine karyotype analysis of the case was normal (46,XX). In the microarray-CGH analysis, de novo 7.7 megabase (Mb) duplication containing 15 morbid OMIM genes including BCL11B gene at 14q32.2-q32.33 locus was detected.

Conclusions: BCL11B, which is highly expressed during the development of T lymphocytes, is a transcriptional regulatory protein. It has been shown immunohistochemically that BCL11B is also expressed in the normal human epidermis. We suggest that the BCL11B gene may be a potential candidate gene for diffuse cutaneous mastocytosis. Other cases with such clinical signs should be examined for mutations of the BCL11B gene.

Keywords: ArrayCGH; BCL11B; chromosome 14q duplication; CTIP2; mastocytosis.

ÖZET

Amaç: Mastositoz, çeşitli organlarda mast hücrelerinin birikmesi ile karakterize heterojen bir klinik fenotip spektrumudur. Kutanöz mastositoz, bu spektrumun deriye sınırlı formudur. Diffüz Kutanöz Mastositoz (DCM), tüm vakaların sadece % 1-3’ünü oluşturan nadir bir kutanöz mastositoz tipidir. Bu çalışmamın amacı, BCL11B (CTIP2) geni...
INTRODUCTION

Mastocytosis is usually a sporadic and heterogeneous group of rare clonal disorders resulting from the expansion and accumulation of neoplastic mast cells and their progenitors in the skin and various internal organs, such as the bone marrow, spleen, lymph nodes and the gastrointestinal tract. It can be limited to the skin known as cutaneous mastocytosis (CM), which is not associated with hematologic disorders and occurs typically as urticaria pigmentosa and has three major subtypes: maculopapular type/urticarial pigmentosa, diffuse cutaneous mastocytosis (DCM) and solitary mastocytoma. Age of onset has a bimodal distribution, with pediatric-onset occurring from birth to 2 years of age and adult-onset occurring in those over age 15. Mastocytosis can also involve extra-cutaneous tissues such as the liver, spleen, bone marrow and lymph nodes as in systemic mastocytosis (SM).

Diffuse cutaneous mastocytosis is a rare variant of CM, accounting for only 1-5% of all cases and occurs mainly at birth or in early infancy. A review of 173 cases of pediatric mastocytosis by Hannaford et al. reported only three cases of DCM. Furthermore, in a study that contains 101 cases of pediatric mastocytosis, all with bullous lesions. In a few cases, particularly in the neonatal diffuse cutaneous form, mastocytosis can be fatal as a result of hypovolemic shock, although infrequent, systemic forms can occur in children. In these cases, the disease may remain active through adolescence as systemic adult mastocytosis. The heterogeneity of clinical presentation in mastocytosis is a result of mast cell (MC) burden and MC activity, the type of skin lesions, the patient’s age at the onset and the associated hematological disorders.

The symptoms of mast cell activation include sudden onset of flush, urticaria, angioedema, pruritus, abdominal pain, headache, diarrhea, hypotension, syncope and musculoskeletal pain which are the results of mast cell mediator release and infiltration into target organs. Blistering generalized erythroderma, nodules and plaques are also observed in some cases of DCM. Only a small proportion of children who do not recover spontaneously before puberty will experience transformation into SM. The amount and variation of the skin lesions, the patient’s age at the onset, and associated hematological disorders make the treatment of the disease challenging. Although considerable research effort has been directed in the past, this complex disease has challenged a clear understanding of pathogenesis. In addition, clinical or biological factors that predict the evolution and severity of the disease in affected children have not been identified yet.

In mastocytosis, the presence of KIT gene mutations in the extracellular, transmembrane, juxta-membrane or activating loop domains, interrupts the normal signaling cascade characterized by constitutive receptor activation independent from stem cell factor. In 90% of cases, mastocytosis is associated with somatic D816V activating mutations of the mast cell growth factor receptor KIT gene in bone marrow MC progenitors. In the case of cutaneous mastocytosis, sporadic D816V activating KIT mutation is found in 20%-40%, while other activating KIT mutations are present in 60%. Moreover, the molecular abnormality of DCM has been associated only with KIT D816F, KIT E839K, KIT D816Y.

Here we aimed to present the molecular characterization of a girl presenting diffuse cutaneous mastocytosis, in which a partial duplication of chromosome 14q was found.

CASE REPORT

A 32 months-old girl was referred to our medical genetic outpatient clinic with a diffuse cutaneous mastocytosis and language delay. The proband...
was the first and the only child of the family and was born from non-consanguineous healthy parents. Prenatal ultrasonographic evaluations revealed an echogenic focus of the brain lateral ventricles but no congenital defect associations were reported at birth. Birth weight and length were 3250 gr and 47cm respectively. She was born by Cesarean section at 38 weeks of gestation after an uneventful pregnancy.

In the neonatal period, the early neurological assessment revealed normal growth and neuromotor development. Additionally, recurrent diarrhea attacks have appeared and the diagnosis of atopic dermatitis was thought because of the clinical appearance. Then it was thought to be a cow’s milk allergy, but symptoms did not improve despite cow’s milk-free diet. The features of diffuse cutaneous mastocytosis, the diffuse bullous lesions with contact in the skin, have been evident in the proband since the 4th month. In the pathological examination of her skin biopsy, it was reported as urticaria pigmentosa and the targeted analysis for D816V mutation of the KIT gene from peripheral blood sample was normal but the clinicians considered her diagnosis as diffuse cutaneous mastocytosis because of her diffuse bullous lesions. She has also chronic anemia despite iron therapy. Her language development was subnormal and stuttering began at 30 months-old, especially when she was excited. There was no history of recurrent bacterial, viral or fungal infections in our patient. In the family history; the uncle of her father and her maternal grandmother exhibited language delay in childhood.

Because of DCM and language delay in the current proband, the routine GTG banded karyotype analyses and Array-CGH (Agilent® Sureprint 180K and Agilent Cytogenomics Software) techniques were used for the chromosomal assessment. Informed written consent was obtained from the parents of the proband. All experiments have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**RESULTS**

GTG-banded metaphases showed a normal karyotype 46,XX after conventional lymphocyte cell culture (Figure 1). The array CGH profiling of the proband showed a *de novo* 7.7 Mb duplication in the 14q32.2-q32.33 locus (Figure 2) that contains 15 morbid OMIM genes (*EML1, YY1, WARS, DYNC1H1, BRF1, INF2, ADSSL1, AKT1, TRAF3, AMN, XRCC3, APOPT1, TECPR2, ZBTB42, BCL11B*). Among them, the *BCL11B* gene was suspected to be responsible for her DCM clinic. Parental karyotypes and array CGH analyses were normal, compared to the current case presenting a partial duplication of chromosome 14q (Figure 3).

**Figure 1:** The karyotype profile of the current proband case was diagnosed as normal 46,XX structure.
**Figure 2:** Shows microarray-CGH profile for chromosome 14 in the current proband case. A de novo 7.7 Mb duplication in 14q32.2-q32.33 were detected in the current mastocytosis case (red circle).

**Figure 3:** Shows the Array CGH triage view for chromosome 14q32.2-q32.33 of the proband (pink), her mother (orange) and father (green).

**DISCUSSION**

Mastocytosis is a group of rare clonal disorders resulting from the expansion of neoplastic mast cells and their progenitors in the skin and various internal organs. Mastocytosis can be systemic or local to the skin. A number of KIT mutations have been detected in patients with CM and SM. Some of these mutations, such as K509I, are more common in pediatric cases, sometimes being detected in germline DNA. Bodemer et al identified several genetic alterations in KIT in a population, some of which have not been identified previously in childhood or adult mastocytosis. These alterations were located mainly in exons 8 and 9 (44% of patients), which encode the fifth Ig (D5) domain and the extracellular region near the transmembrane domain, regions that have previously been shown to be affected in core-binding factor-acute myeloid leukemia and in gastrointestinal stromal tumor; respectively.
Previous studies suggest that it is a result of the absence of genetic alterations within KIT in some mastocytosis patients. This implies that these patients have alterations in proteins other than KIT that regulate mast cell proliferation and function. In general, these results confirm that familial childhood-onset mastocytosis can occur both in the presence and in the absence of KIT mutations. They performed a multicenter study to examine the association of c-KIT mutations with childhood-onset mastocytosis and found the D816V mutation (exon 17), which is frequently associated with adult mastocytosis in 18 of 50 (36%) children in this study. Three additional patients (6%) had other mutations in codon 816, including two with a D816Y mutation and one with a previously unreported D816I mutation. As with the D816V mutation, they found that both the D816Y and D816I mutations cause a ligand-independent activation of KIT.

Recently, it was found that the mastocytosis phenotype may be linked to abnormalities in GPCR downstream targeting due to G protein beta subunit activation. Szczałuba et al. described a case of the condition with manifestations of cutaneous mastocytosis associated with a novel de novo mutation GNB1 NM_00128539.1: c.230G>T; p.(Gly77Val). They also present the immunohistochemical evidence that has been shown to regulate transcription through interaction with COUP-TF nuclear receptor proteins as well as through direct, sequence-specific DNA binding. It is a transcriptional regulatory protein that is highly expressed in and plays a critical role(s) during the development of T lymphocytes, the central nervous system and it is also highly expressed in the skin during embryogenesis and in adulthood as revealed by immunohistochemical analyses. The mutations of the BCL11B gene are reported to cause Immunodeficiency-49 (IMD49) and also associated with the intellectual development disorder with speech delay, dysmorphic facies and T cell abnormalities (IDDSFTA; 618092), both of these disorders are inherited with autosomal dominant manner. It was shown that CTIP2 is also expressed in layer V of the cerebral cortex and plays a critical role in the establishment of connections of corticospinal motor neurons to the spinal cord. In their study, Ganguli-Indra et al. have demonstrated by immunohistochemistry that BCL11B is expressed in normal human epidermis. Enhanced expression of CTIP2 was observed in hyperproliferative skin of atopic dermatitis and allergic contact dermatitis patients. It is likely that an optimum level of CTIP2 expression is required for the maintenance of skin homeostasis. An increase in CTIP2 expression might lead to an increase in epidermal proliferation and subsequently altered differentiation in atopic dermatitis (AD) and/or allergic contact dermatitis skin. Duplication in the 14q32.2-32.3 region was reported to be associated with primordial short stature, mild developmental delay and distinct facial dysmorphism which were absent in our patient. But absence of BCL11B gene located in this region was reported to be associated with AD-like skin inflammation and extensive infiltration of immune cells including mast cells in adult mice skin, as well as systemic immune responses that share similarity with human AD patients, consistent with DCM clinic of our patient.

CONCLUSION

Mastocytosis is an important disease that affects the social life of the patient. The increase in mast cell mediators can be triggered by sudden heat change, scrubbing/friction, excessive sweating, heavy physical exercise, intense UV light exposure, stress, fear and some medications. It’s a worrying health risk for patients and their families. These patients need to carry epinephrine with them all day. In the presented case report it was suggested that the BCL11B gene is a candidate gene for diffuse cutaneous mastocytosis. This finding may shed light on research into pharmacological agents that reduce BCL11B gene expression for the treatment of DCM. Further analysis is required for any other possible genetic changes that may be related to the...
patient's clinic and this association needs to be supported by research results involving multiple cases.

**Declarations**

**Ethics approval and consent to participate**
All experiments have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**Consent for publication**
Informed written consent was obtained from the parent of the proband for the genetic analyses and the publication, separately.

**Availability of data and material**
All data generated or analyzed during this study are included in this published article.

**Competing interests**
The authors declare that they have no competing interests.

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**Authors' contributions**
F.S., B.A. and M.O.; acquisition of data, analyzed the clinical data and designed the clinical experiments, F.S., O.Y., M.O., and R.B.; designed the experiments, performed PCR, analyzed the sequencing data, B.A. and R.B.; wrote the manuscript. O.O.; interpretation of data, supervised the study and review the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Arock M, Valent P. Pathogenesis, classification, and treatment of mastocytosis: state of the art in 2010 and future perspectives. Expert Rev Hematol 2010; 3:497–516.
2. Szczalubaa K, Biernacka A, Szymańskiak K, Gasperowicza P, Kosińska J, Rydzanicza M, Płoskia R. Novel GNB1 de novo mutation in a patient with neurodevelopmental disorder and cutaneous mastocytosis: Clinical report and literature review. European Journal of Medical Genetics 2018; 61: 157–160.
3. Valent P, Akin C, Hartmann K, Nilsson G, Reiter A, Hermine O, et al. Advances in the classification and treatment of mastocytosis: current status and outlook toward the future. Cancer Res 2017; 77(6): 1261–70.
4. Hosking A-M, Makdisi J, Ortenzio F, de Feraudy S, Smith J, Linden K. Diffuse cutaneous mastocytosis: Case report and literature review. Pediatr Dermatol 2018; 00:1–5.
5. Méni C, Bruneau J, Georgin-Lavialle S, et al. Paediatric mastocytosis: a systematic review of 1747 cases. Br J Dermatol 2015; 172 (3):642-651.
6. Hannaford R, Rogers M. Presentation of cutaneous mastocytosis in 173 children. Australas J Dermatol 2001; 42(1):15-21.
7. Lange M, Niedoszytko M, Niedoszytko B, Łata J, Trzeciak M, Biernat W. Diffuse cutaneous mastocytosis: analysis of 10 cases and a brief review of the literature. J Eur Acad Dermatol Venereol 2012; 26 (12):1565-1571.
8. Bodemer C, Hermine O, Palme 'rini F, YangY, et al. Pediatric Mastocytosis is a Clonal Disease Associated with D816V and Other Activating c-KIT Mutations. Journal of Investigative Dermatology 2010; 130: 804–815.
9. Kushnir-Sukhov NM, Brittain E, Scott L, Metcalfe DD. Clinical correlates of blood serotonin levels in patients with mastocytosis. Eur J Clin Investig 2008; 38(12):953–958.
10. Carter MC, Metcalfe DD, Komarov HD. Mastocytosis. Immunol Allergy Clin N Am 2014; 34(1):181–196.
11. Edwards AM, Capkova S. Oral and topical sodium cromoglicate in the treatment of diffuse cutaneous mastocytosis in an infant. BMJ Case Rep 2011; 29:2011.
12. Komi A D E, Rambasek T, Wöhrl S. Mastocytosis: from a Molecular Point of View. Clinic Rev Allerg Immunol 2018; 54:397–411.
13. Cardet JC, Akin C, Lee MJ. Mastocytosis: update on pharmacotherapy and future directions. Expert Opin Pharmacother 2013; 14(15):2033–2045.
14. Valent P. Diagnosis and management of mastocytosis: an emerging challenge in applied hematology. Hematology Am Soc Hematol Educ Program 2015; 2015:98-105.
15. Wilcock A, Bahri R, Bulfone-Paus S, Arkwright PD. Mast cell disorders: From infancy to maturity. Allergy 2019; 74:53–63.

16. Valent P. Mastocytosis: a paradigmatic example of a rare disease with complex biology and pathology. Am J Cancer Res 2013; 3(2):159–172.

17. Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattan C, Brockow K, et al. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. Allergy 2014; 69:1267–74.

18. Arock M, Sotlar K, Akin C, Broesby-Olsen S, Hoermann G, Escribano L, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia 2015; 29:1223–32.

19. Gari M, Goodeve A, Wilson G, Winship P, Langabeer S, Linch D, et al. C-kit proto-oncogene exon 8 in-frame deletion plus insertion mutations in acute myeloid leukaemia. Br J Haematol 1999; 105:894–900.

20. Lux ML, Rubin BP, Biase TL, Chen CJ, Maclure T, Demetri G, et al. KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. Am J Pathol 2000; 156:791–5.

21. Longley BJ Jr, Metcalfe DD, Tharp M, Wang X, Tyrrell L, Lu SZ, et al. Activating and dominant inactivating c-KIT catalytic domain mutations in distinct clinical forms of human mastocytosis. Proc Natl Acad Sci USA 1999; 96:1609–14.

22. Valent P, Akin C, Sperr WR, Escribano L, Arock M, Horny HP, et al. Aggressive systemic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria. Leuk Res 2003; 27:635–41.

23. Subramanian H, Gupta K, Ali H. Roles of MAS-related G protein-coupled receptor- X2 (MRGPRX2) on mast cell-mediated host defense, pseudoallergic drug reactions and chronic inflammatory diseases. J allergy Clin Immunol 2016; 138 (3): 700–710.

24. Yoda A, Adelman G, Tamburini J, et al. Mutations in G protein beta subunits promote transformation and kinase inhibitor resistance. Nat Med 2015; 21 (1): 71–75.

25. Fujisawa D, Kashiwakura J, Kita H, Kikukawa Y, Fujitani Y, Sasaki-Sakamoto T, et al. Expression of Mas-related gene X2 on mast cells is upregulated in the skin of patients with severe chronic urticaria. J Allergy Clin Immunol 2014; 134: 622–633 e9.

26. Lyons JJ, Hughes JD, Le QT, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet 2016; 48:1564-1569.

27. Avram D, Fields A, Senawong T, Topark-Ngarm A, Leid M. (2002). COUP-TF (chicken ovalbumin upstream promoter transcription factor)-interacting protein 1 (CTIP1) is a sequence-specific DNA binding protein. Biochem J: 368: 555–563.

28. Golonzhka O, Leid M, Indra G, Indra AK. Expression of COUP-TF-interacting protein 2 (CTIP2) in mouse skin during development and in adulthood. Gene Expression Patterns 2007; 7:754–760.

29. Ganguli-Indra G, Liang X, Hyter S, Leid M, Hanifin J, Indra AK. Expression of COUP-TF-interacting protein 2 (CTIP2) in human atopic dermatitis and allergic contact dermatitis skin. John Wiley & Sons A/S, Experimental Dermatology 2009; 18, 994–996.

30. Wang Z, Zhang L, Guha G, Li S, Kyrylvkova K, Kioussi C, Indra AK. Selective ablation of Ctip2/Bcl11b in epidermal keratinocytes triggers atopic dermatitis-like skin inflammatory responses in adult mice. PloS one 2012; 7(12): e51262.