J Cutan Pathol 2016: 43: 388–393
doi: 10.1111/cup.12651
John Wiley & Sons. Printed in Singapore

© 2015 John Wiley & Sons A/S.
Published by John Wiley & Sons Ltd

Journal of
Cutaneous Pathology

Pseudoangiomatous xanthelasmoid mastocytosis: two case reports showing the hypervascularity of this rare variant of cutaneous mastocytosis

Xanthelasmoid mastocytosis or xanthelasmoidea is a rare clinical variant of cutaneous mastocytosis characterized by a yellow hue of the clinical lesions, which are often misdiagnosed as juvenile xanthogranuloma. We present two pediatric cases of xanthelasmoid mastocytosis presenting as isolated mastocytomas, which are notable histopathologically for their hypervascularity. This pseudoangiomatous variant of cutaneous mastocytosis is important for pathologists to have knowledge of, so that a diagnosis of a vascular tumor is not rendered accidentally. The yellow hue has previously been explained by the usual deep and solid dermal mast cell infiltrate. In the two presented cases, however, the mast cell infiltrate was sparse, and the yellow color cannot be related to infiltrate density. We believe that the hypervascularity is at least one factor in the production of clinical xanthelasmoid appearance, and we propose the term 'pseudoangiomatous xanthelasmoid mastocytosis' to properly describe this rare variant of cutaneous mastocytosis.

Keywords: hypervascularity, mastocytosis, vascular tumor

Kolivras A, André J, Thompson C, Sass U, Fraitag S. Pseudoangiomatous xanthelasmoid mastocytosis: two case reports showing the hypervascularity of this rare variant of cutaneous mastocytosis.
J Cutan Pathol 2016; 43: 388–393. © 2015 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

Athanassios Kolivras[1], Josette André[1], Curtis Thompson[2,3,4], Ursula Sass[1] and Sylvie Fraitag[5]

[1]Department of Dermatology and Dermatopathology, Saint-Pierre, Brugmann and HUDERF Hospitals, Université Libre de Bruxelles, Brussels, Belgium,
[2]Department of Biomedical Engineering, Oregon Health Sciences University, Portland, OR, USA,
[3]Department of Pathology, Oregon Health Sciences University, Portland, OR, USA,
[4]Department of Dermatology, Oregon Health Sciences University, Portland, OR, USA, and
[5]Department of Pathology, hôpital Necker-Enfants Malades, APHP, Paris, France

Athanassios Kolivras, MD
Departments of Dermatology and Dermatopathology, Saint-Pierre, Brugmann and HUDERF Hospitals, Université Libre de Bruxelles, Brussels, Belgium
Tel: +32.(0)2.5354379
Fax: +32.(0)2.5354381
e-mail: kolivras@gmail.com

Accepted for publication November 7, 2015

Xanthelasmoid mastocytosis or xanthelasmoidea is a rare clinical variant of cutaneous mastocytosis described in 1875 by Tilbery and in 1883 by Fox.[1,2] Xanthelasmoid mastocytosis is so named because of the yellow hue of clinical lesions. The lesions occur most frequently in children. The main clinical differential diagnoses in xanthelasmoid mastocytosis is juvenile xanthogranuloma, xanthoma or congenital melanocytic nevus.[3–5] Xanthelasmoid mastocytosis does not have any prognostic significance, with no increased risk for systemic involvement.[6]

We present two pediatric cases of xanthelasmoid mastocytosis presenting as isolated mastocytomas, which are notable histopathologically for their hypervascularity. Pathologists should

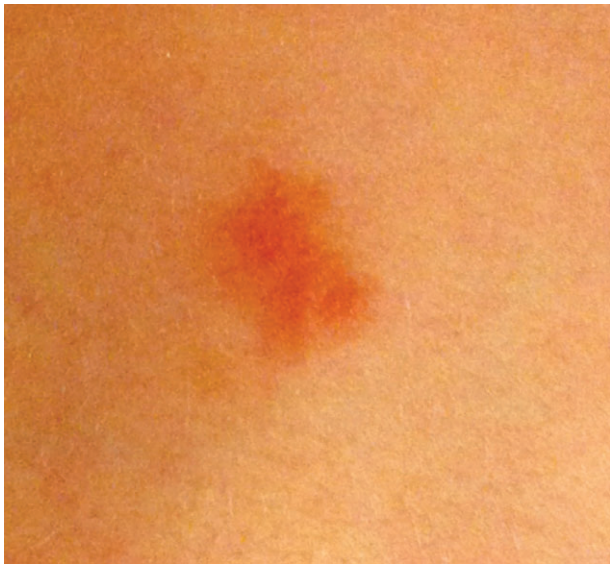

Fig. 1. The plaque was red, yellow and brown centrally and yellow at the periphery.

be aware of this clinical and histopathologic variant, so that they do not misdiagnose xanthelasmoid mastocytosis as a hemangioma, and, thus, we propose the term 'pseudoangiomatous xanthelasmoid mastocytosis' to properly describe this rare variant of cutaneous mastocytosis.

Case reports

Case 1

An 8-year-old boy presented with a 2-cm slightly infiltrated plaque on the right chest, present since birth. The plaque was red, yellow and brown centrally and yellow at the periphery (Fig. 1). Dermoscopic examination showed combined features of both the reticular vascular and yellow blot pattern.[7] The clinical differential diagnosis included plaque-type juvenile xanthogranuloma, smooth muscle hamartoma, connective tissue hamartoma and mastocytoma. A positive Darier sign provided evidence that this was a mastocytoma. On biopsy, low-power examination showed a proliferation of thin-walled, dilated vessels in the papillary and superficial reticular dermis, set in a slightly fibrotic stroma (Fig. 2). On higher magnification, there was hyperpigmentation of the epidermal basalis with papillary dermal melanophages (pigmentary incontinence). The papillary and superficial reticular dermis contained a mononuclear cell infiltrate with admixed eosinophils. The monocytes were slightly pleomorphic, oval and polygonal in shape, with moderately abundant

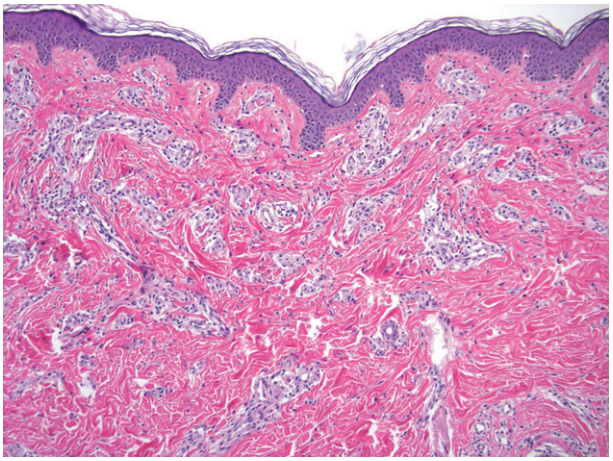

Fig. 2. Proliferation of thin-walled and dilated vessels in the papillary and superficial reticular dermis, set in a slightly fibrotic stroma.

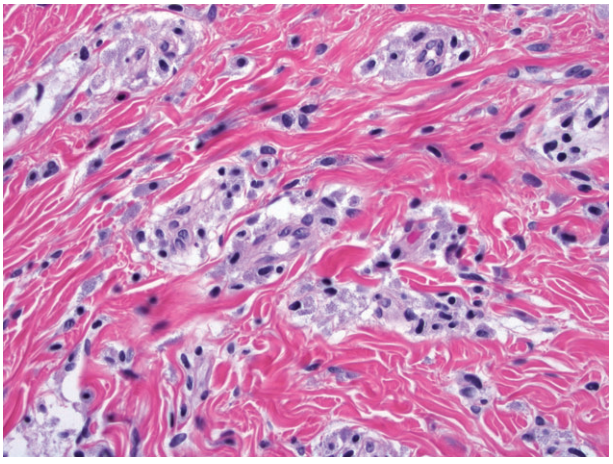

Fig. 3. The mast cells were slightly pleomorphic, oval and polygonal in shape, with moderately abundant and slightly pink-staining cytoplasm.

and slightly pink-staining cytoplasm (Fig. 3). Giemsa and toluidine blue stains highlighted metachromatic granules within the cytoplasm (Fig. 4). The mast cells were also positive staining with a CD117 (Ckit antibody) immunohistochemical study. A Perls iron stain did not reveal any hemosiderin pigment. A Glut-1 immunostain was negative. Thus, a diagnosis of cutaneous mastocytoma was made.

Case 2

A newborn, girl presented with a slightly infiltrated plaque located on the abdomen showing heterogeneous yellow-brown pigmentation, most consistent clinically for a congenital-type melanocytic nevus (Fig. 5). A biopsy showed, on low power, numerous,

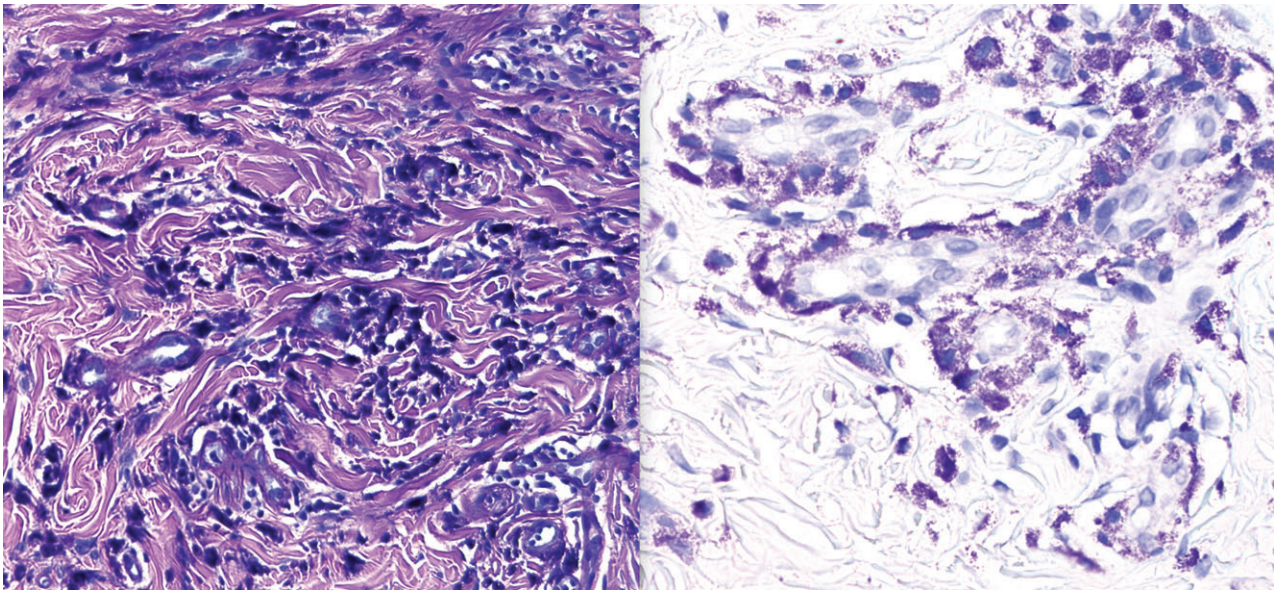

Fig. 4. Giemsa (left) and toluidine blue (right) stains highlighted metachromatic granules within the cytoplasm of mononuclear cells.

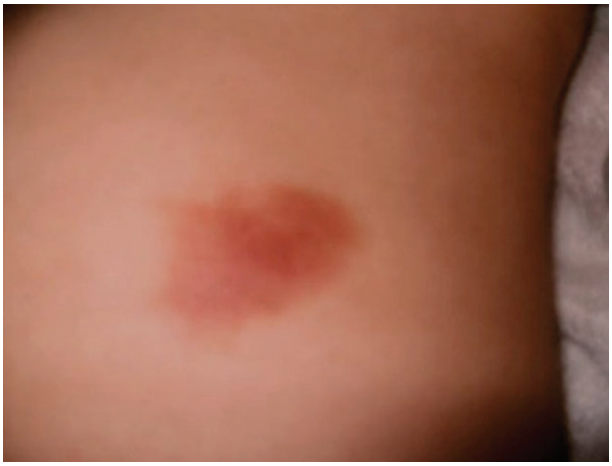

Fig. 5. Infiltrated plaque showing heterogeneous yellow-brown pigmentation.

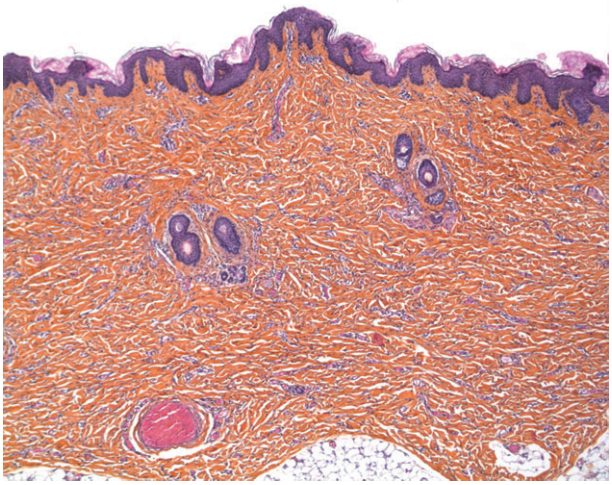

Fig. 6. Numerous, thin-walled, small-diameter vessels set in a fibrotic dermis.

thin-walled, small-diameter vessels set in a fibrotic dermis (Fig. 6). The vessels ranged from very small-diameter to mid-sized venules. On higher magnification, stellate cells, not easily identifiable as mast cells, were present between the venules (Fig. 7). Besides the stellate cells, there was no infiltrate of either mononuclear cells or eosinophils. A toluidine blue stain and CD117 immunohistochemical study showed strong positivity of the stellate cells, consistent with diagnosis of cutaneous mastocytoma (Fig. 8). Both the Perls iron stain and the Glut-1 immunostain were negative. After the biopsy at the age of 9 months, the lesion started to clinically regress.

Discussion

We present two cases of cutaneous mastocytosis with unique and rare clinical and histopathologic features, a xanthelasmoid clinical appearance and a hypervascular, pseudoangiomatous histopathologic appearance. The pseudoangiomatous findings have not previously been reported in xanthelasmoid mastocytosis.

The clinical xanthelasmoid appearance is shown well in these two cases. The yellow hue usually present in xanthelasmoid mastocytosis is usually explained by the usual deep and solid dermal mast cell infiltrate.[1,3,4,8] In the two cases

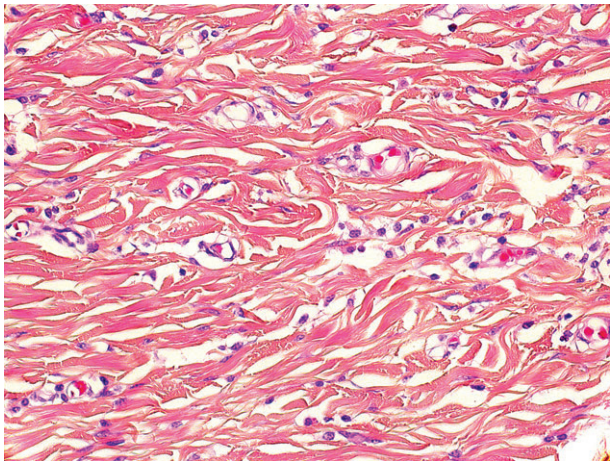

Fig. 7. On higher magnification, stellate cells were present between the vessels.

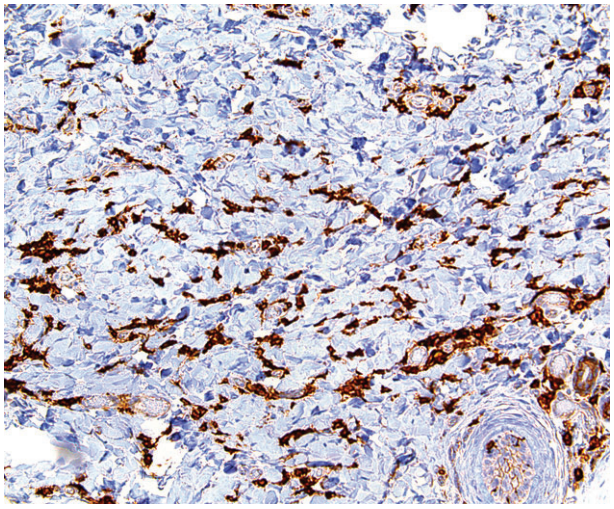

Fig. 8. CD117 immunohistochemical study showed strong staining of the stellate cells.

presented, however, the mast cell infiltrate was sparse, and the yellow color cannot be related to infiltrate density. Thus, the yellow hue should have another histopathological explanation, and we propose that the hypervascularity is at least one factor in the production of the clinical xanthelasmoid appearance. The first of the two cases also had a red component to the central portion of the lesion, most certainly the result of the hypervascularity.

Although most cases of xanthelasmoid mastocytosis are the maculopapular and nodular variants of cutaneous mastocytosis,[4,8–10] xanthomatous mastocytosis has also been reported in other variant of cutaneous mastocytosis. There is one case report of severe generalized nodular and bullous mastocytosis in a 7-month-old boy,[6] and blistering has also been reported separately in xanthelasmoid mastocytosis.[6,11] Eruptive nodules with cerebriform or 'peau d'orange' surface have been described in a 20-year-old female.[5] Xanthelasmoid mastocytosis has also been misdiagnosed as pseudoxanthoma elasticum.[1,12,13] An association with plane xanthomas[14] and anetoderma have also been reported.[9] Xanthelasmoidea has never been described to be manifested as telangiectasia macularis eruptiva perstans (TMEP) or diffuse cutaneous mastocytosis.

This pseudoangiomatous variant of cutaneous mastocytosis is important for dermatologists and pathologists to have knowledge of because of this striking and misleading histopathological feature, which is shown well with these two cases, both of which could have been misdiagnosed as a vascular tumor.

Increased vascularity in cutaneous mastocytosis may be the result of mast cells release of potent proangiogenic factors such as histamine, vascular endothelial growth factor, basic fibroblast growth factor, transforming growth factor β, tumor necrosis factor-α and interleukin-8 and the extracellular proteoglycan perlecan. Mast cell enzymes, like metaloproteinases, tryptase and chymase also participate in vessel formation.[15–18]

Mast cell hyperplasia is also typically seen in hemangiomas, particularly in proliferating hemangiomas, as well as in arteriovenous and capillary malformations.[19–23] The presence of mast cells in these tumors and malformations should not erroneously lead to the diagnosis of mastocytosis. However, in the reported cases, cutaneous lesions were present at birth and mast cells are not found in a congenital hemangioma. In addition, a congenital hemangioma is characterized by well-defined, variably sized lobules containing well-differentiated small capillaries, being centered by draining vessels and surrounded by a fibrous stroma. Large dilated vessels are also present in the non-involuting variant. Infantile hemangiomas are not usually present at birth, except in cases of abortive infantile hemangioma. This diagnosis has been excluded in both cases by the negative Glut-1 immunostain. In addition, diagnosis of proliferative stage of infantile hemangioma can easily be ruled out in both cases by the presence of well-differentiated vessels scattered in the conjunctive tissue. Mast cells seen in the stroma of vascular lesions are usually easily recognizable and do not require any special stain to highlight them because they are round, with a pink cytoplasm and a dense, round, central nucleus. On

the contrary, the second case had only stellate mast cells that could not be recognizable as mast cells on the Hematoxylin and Eosin (H&E) slide. Arteriovenous and capillary malformations have distinctive histopathological findings and are, therefore, excluded in the differential diagnosis. Darier sign, which was positive in the first case, is never seen in hemangiomas and in vascular malformations.

Although our first case had a red component to the lesion clinically that we attribute to hypervascularity, the hypervascularity of cutaneous mastocytosis is often not observed clinically and only identified histopathologically. Hypervascularity is certainly known to be present in other variant of cutaneous mastocytosis, such as TMEP.

Dermoscopic examination of TMEP is characterized by a reticular vascular pattern. The same dermoscopic pattern is found in a small proportion of maculopapular mastocytosis. The yellow blot dermoscopic pattern is frequently observed in solitary mastocytoma.[7] As previously mentioned, dermoscopic examination of the first presented case showed combined features of both the reticular vascular and yellow blot pattern. We believe that the reticular vascular pattern is the result of the thin telangiectasias within the papillary dermis, and the yellow blot pattern is the result of the vascular proliferation within the reticular dermis with associated fibrosis. When hypervascularity in the reticular dermis is pronounced, the yellow hue is clinically apparent. This could explain why xanthelasmoidea has never been reported in macular lesions, such as TMEP. The yellow color cannot be explained by presence of hemosiderin, because of negativity of Perls stain in both presented cases. The presence of hypervascularity is not a risk factor of progression to systemic disease, and, therefore, xanthelasmoidea does not have any prognostic significance.

Xanthelasmoid mastocytoma could also be related to the so-called 'fibrous mastocytoma' characterized by diffuse proliferation spindle and ovoid mast cells and fibroblasts, which are closely packed and are separated by collagen and elastic fibers, forming ill-defined intersecting bundles. The authors also describe irregularly oriented vessels, in contrast to the vertical orientation observed in scar tissue. Our two presented cases showed similar stromal changes, but lacked the dense proliferation of mast cells.[24]

In our experience, dilated vessels with more or less vascular proliferation are always present upon histopathological examination in all forms of cutaneous mastocytosis, and, therefore, vascularity is a very helpful diagnostic clue. Other histopathological clues include the presence of eosinophils and epidermal basal layer hyperpigmentation, although these features are quite often lacking histopathologically.[25]

Conclusion

We present a novel description of the hypervascularity present in xanthelasmoid mastocytoma, showed well with these two cases. This pseudoangiomatous feature is an important feature for both dermatologists and pathologists to appreciate, so that a diagnosis of a vascular tumor is not rendered accidentally. In addition, these two cases provide evidence that the clinical xanthelasmoid (yellow) appearance is likely produced in part from the hypervascularity. Our proposed term 'pseudoangiomatous xanthelasmoid mastocytosis' accommodate both of these features of well and allows for more accurate clinical and histologic diagnosis.

Acknowledgements

We would like to thank Dr Carole Bonneau for her contribution in case 2.

References

1. Griffiths WA, Daneshbod K. Pseudoxanthomatous mastocytosis. Br J Dermatol 1975; 93: 91.
2. Fox TC. On urticaria pigmentosa or xanthelasmoidea; urticaria pigmentosa (sangster), u. perstans pigmentosa (pick), xanthelasmoidea (tilbury fox). Med Chir Trans 1883; 66: 329.
3. Tesnière A, Stefan A, Desdoits A, Comoz F, Dompmartin A, Verneuil L. Mastocytose xanthélasmoïde infantile. Ann Dermatol Venereol 2015; 42: 381.
4. Revert A, Jordá E, Ramón D, Verdeguer JM, Torres V, Pitarch A. Xanthelasmoid mastocytosis. Pediatr Dermatol 1991; 8: 152.
5. Chraibi H, Belgnaoui F, Benessahraoui M, Mirrane H, Mansouri F, Hassam B. Mastocytose xanthelasmoidea de l'adulte. Ann Dermatol Venereol 2008; 135: 87.
6. Husak R, Blume-Peytavi U, Pfrommer C, Geilen CC, Goerdt S, Orfanos CE. Nodular and bullous cutaneous mastocytosis of the xanthelasmoid type: case report. Br J Dermatol 2001; 144: 355.
7. Vano-Galvan S. Dermoscopic features of skin lesions in patients with mastocytosis. Arch Dermatol 2011; 147: 932.
8. Rasmussen JE. Xanthelasmoidea. An unusual case of urticaria pigmentosa. Arch Dermatol 1976; 112: 1270.
9. Pérez-Pérez L, Allegue F, Caeiro J, Fabeiro J, Rodríguez A, Zulaica A. Coexistence of two types of clinical lesions in childhood-onset mastocytosis. Indian J Dermatol Venereol Leprol 2011; 77: 184.
10. Loubeyres S, Leaute-Labreze C, Roul S, Labbe L, Bioulac-Sage P, Taïeb A. Classification et prise en charge des mastocytoses de l'enfant. Ann Dermatol Venereol 1999; 126: 20.
11. Haneke E. Kasuistischer Beitrag zur Behandlung der Urticaria pigmentosa xanthelasmoidea bullosa mit Cyproheptadin. Dermatology 1970; 141: 247.

12. Mazereeuw-Hautier J, Vind-Kezunovic D, Barrié L, Bonafé J-L. Xanthelasmoid mastocytosis in flexural aereas. Pediatr Dermatol 2004; 21: 520.
13. Niemi KM, Karvonen J. A case of pseudoxanthomatous mastocytosis. Br J Dermatol 1976; 94: 343.
14. Matsumoto M, Ikeda M, Takeya M, Kodama H. Plane xanthoma associated with multiple mastocytoma. Pediatr Dermatol 2007; 24: 66.
15. Ribatti D, Ranieri G. Tryptase, a novel angiogenic factor stored in mast cell granules. Exp Cell Res 2015; 332: 157.
16. Gaber MA, Seliet IA, Ehsan NA. Mast cells and angiogenesis in wound healing. Anal Quant Cytopathol Histpathol 2014; 36: 32.
17. Ammendola M, Leporini C, Marech I, et al. Targeting mast cells tryptase in tumor microenvironment: a potential antiangiogenetic strategy. Biomed Res Int 2014; 6: 154702.
18. Dyduch GG, Kaczmarczyk KK, Okoń KK. Mast cells and cancer: enemies or allies? Pol J Pathol 2012; 63: 1.
19. Buhl T, Shoukier M, Grzmil P, Revencu N, Schön MP, Seitz CS. Multifocal capillary malformations due to RASA1 mutation misdiagnosed as cutaneous mastocytosis. Arch Dermatol 2012; 148: 1334.
20. Pawane P, Anshu , Gangane N. Hemangiomas versus arterio-venous malformations: role of elastic stains and mast cell density. Indian J Pathol Microbiol 2014; 57: 191.
21. Burrows PE, Mulliken JB, Fellows KE, Strand RD. Childhood hemangiomas and vascular malformations: angiographic differentiation. AJR Am J Roentgenol 1983; 141: 483.
22. Koutlas IG, Jessurun J. Arteriovenous hemangioma: a clinicopathological and immunohistochemical study. J Cutan Pathol 1994; 21: 343.
23. Glowacki J, Mulliken JB. Mast cells in hemangiomas and vascular malformations. Pediatrics 1982; 70: 48.
24. Wood C, Sina B, Webster CG, Kurgansky D, Drachenberg CB, Reedy EA. Fibrous mastocytoma in a patient with generalized cutaneous mastocytosis. J Cutan Pathol 1992; 19: 128.
25. Fraitag S. Mastocytoses cutanées. Ann Dermatol Venereol 2007; 134: 589.