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Editorial's comment to the article

Granular cell tumor of the perineum (clinical case), Rais R. Shakirov, Oleg Yu. Karpukhin, Marat I. Ziganshin, Ivan S. Raginov

The published article presents a clinical case of granular cell tumor of the perianal region, which is a rare neoplasm, so the presented case is undoubtedly of practical interest. However, the literature data and description of the tumor presented in the paper require, in my opinion, some clarification.

Granular cell tumor can occur at any age, mainly at 40–60 years with a predominance of male patients (male/female ratio is 2–3:1). The malignant variant of the tumor occurs at a younger age (40 years) and more often in women. Typical tumor site is the skin and subcutaneous tissue of the head, neck, torso and upper extremities. In 25% of cases, the tumor is located in the tongue, in 5–15% of cases it affects the mammary glands. Sometimes it can be located in the gastrointestinal tract (esophagus, colon, perianal region) and respiratory tract (larynx, trachea). In most cases, granular cell tumor is represented by a solitary node, but multifocal tumor growth is possible in 10% of cases affecting one or more anatomical areas or organs [1–4]. Unfortunately, the authors did not clearly describe the tumor site, which preoperatively was located in perianal region, intraoperatively — it came from the low rectum wall and in the morphological report the structure of the tumor is described in the fatty tissue with the involvement of the dermis.

It should be noted that, indeed, one of the first descriptions of this tumor located in the tongue was made in 1926 by Russian pathologist A.I. Abrikosov, who believed that the tumor was of myogenic origin. The term "Abrikosov tumor" is used in the Russian literature and is not included in the WHO international classification of tumors [5]. The theory about the degenerative and metabolic origin of this neoplasm, which is mentioned in the article, is currently not proven and not generally accepted. According to recent concepts, a granular cell tumor is a true tumor with neuroectodermal differentiation and in the latest WHO tumor classification is included in the group of peripheral nerve tumors in the form of two options — benign and malignant [5]. The development of granular cell tumors is associated with dysfunction of V-ATPase associated genes, such as ATP6AP1 (61%) and ATP6AP2 (11%), in which loss-of-function mutations are found in 72% of granular cell tumors, regardless of its location and histological subtype (benign or malignant). It is believed that inactivation of these genes in Schwann cells leads to the accumulation of granules in the cytoplasm, the ultrastructure and immunophenotype of which corresponds to endosomes. Although the mechanism of gene dysfunction and protein accumulation in the cytoplasm of cells is currently not fully known, mutation of the ATP6AP1 and ATP6AP2 genes is considered pathognomonic for this tumor [5–7].

The presented clinical case describes the slow growth of the tumor, which is peculiar for this pathology. The tumor, as a rule, has a long asymptomatic course, with the exception of the tumor site in the skin, subcutaneous tissue and tongue. In clinical and instrumental checkup, the tumor is a nodular neoplasm without specific signs, therefore the main diagnosis of granular cell tumor is carried out by morphology. The paper contains photographs of a gross specimen of the tumor and its histological structure (at different magnifications), however, the description of the tumor morphology is quite formal, although it is the characteristic histological picture and the immunophenotype of the tumor that allows the correct diagnosis to be made.

Macroscopically, the tumor is a poorly demarcated, pale-yellow node. The size of the tumor, according to the literature, can range from 0.5 to 18 cm (in most cases up to 3 cm, the malignant version is usually larger, more than 5 cm in its greatest size). Histologically, the tumor is represented by nests or trabeculae of large epithelioid cells with well-defined eosinophilic cytoplasm with the presence of a large number of granules with a characteristic rim of clearing along the periphery (haloes), contained in lysosomes, which determined the name of the tumor. The main diagnostic immunohistochecmical markers are positive staining of tumor cells with antibodies to S100, SOX10, in addition, tumor cells are positively stained with antibodies to

nestin, inhibin and calretinin {2437,531}, acytoplasmic lysosomal inclusions are positive when stained with antibodies to CD68, CD63 (NKI/C3) and NSE. It should be noted that the malignant variant of the tumor is very rare and is characterized by more pronounced cellularity, cell polymorphism, a high level of mitotic activity (more than 2 mitoses per 2 mm^2) and the presence of areas of tumor necrosis, while the proliferation index Ki67, as indicated in the paper, has no diagnostic or prognostic value. To exclude recurrence, curative removal of the tumor and post-op follow up is necessary, especially with a malignant variant of the tumor, in which there is a high risk of metastatic disease (up to 50% of cases), which, in combination with the large size of the tumor and the elderly age of the patients, is considered an unfavorable prognostic factor [5,8–12].

It is important to note that for clinicians, the diagnosis of a granular cell tumor should prompt further sophisticated and deep diagnostic checkup of the patient, since this tumor may be multiple and/or be associated with a number of hereditary syndromes, such as neurofibromatosis type 1, Noonan, LEOPARD syndromes (syndromes with multiple congenital anomalies). internal organs, skeleton, etc.), especially in young patients [13–15].

In conclusion, it should be emphasized that the clinical diagnosis of non-epithelial tumors of the gastrointestinal tract is quite complicated, however, practitioners need to remember this group of tumors when carrying out differential diagnosis and choosing surgical approach. Determination of the histological type, degree of malignancy and prognostic factors is possible only with morphological examination and immunophenotyping of the tumor using appropriate diagnostic criteria.

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REFERENCES

1. Singhi AD, Montgomery EA. Colorectal granular cell tumor: a clinicopathologic study of 26 cases. *Am J Surg Pathol*. 2010 Aug;34(8):1186–92.
2. Melo CR, Melo IS, Schmitt FC, et al. Multicentric granular cell tumor of the colon: report of a patient with 52 tumors. *Am J Gastroenterol*. 1993;88(10):1785–1787.
3. van der Maten J, Blaauwgeers JL, Sutedja TG, et al. Granularcell tumors of the tracheobronchial tree. *J Thorac Cardiovasc Surg*. 2003 Sep;126(3):740–3.
4. Lack EE, Worsham GF, Callihan MD, et al. Granular cell tumor: a clinicopathologic study of 110 patients. *J Surg Oncol*. 1980;13(4):301–316. doi: 10.1002/jso.2930130405
5. Lokuhetty D, White V, Cree IA. WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. *Lyon (France): International Agency for Research on Cancer*. 5th ed., vol. 3. 2020. https://publications.iarc.fr/588.
6. Pareja F, Brandes AH, Basili T, et al. Loss-of-function mutations in ATP6AP1 and ATP6AP2 in granular cell tumors. *Nat Commun*. 2018 Aug 30;9(1):3533.
7. Sekimizu M, Yoshida A, Mitani S, et al. Frequent mutations of genes encoding vacuolar H + -ATPase components in granular cell tumors. *Genes Chromosomes Cancer*. 2019 Jun;58(6):373–80.
8. Fanburg-Smith JC, Meis-Kindblom JM, Fante R, et al. Malignant granular cell tumor of soft tissue: diagnostic criteria and clinicopathologic correlation. *Am J Surg Pathol*. 1998 Jul;22(7):779–94.
9. Fanburg-Smith JC, Meis-Kindblom JM, Fante R, Kindblom LG. Malignant granular cell tumor of soft tissue:diagnostic criteria and clinicopathologic correlation. *Am J Surg Pathol*. 1998;22(7):779–794. doi: 10.1097/00000478-199807000-00001
10. Wang J, Zhu XZ, Zhang RY. Malignant granular cell tumor: a clinicopathologic analysis of 10 cases with review of literature. *Zhonghua Bing Li Xue Za Zhi*. 2004 Dec;33(6):497–502. Chinese.
11. Vered M, Carpenter WM, Buchner A. Granular cell tumor of the oral cavity: updated immunohistochemical profile. *J Oral Pathol Med*. 2009;3818(1):150–159. doi: 10.1111/j.1600-0714.2008.00725.x
12. Parfitt JR, McLean CA, Joseph MG, et al. Granular cell tumours of the gastrointestinal tract: expression of nestin and clinicopathological evaluation of 11 patients. *Histopathology*. 2006;48(4):424–430.
13. Ramaswamy PV, Storm CA, Filiano JJ, et al. Multiple granular cell tumors in a child with Noonan syndrome. *Pediatr Dermatol*. 2010 Mar-Apr;27(2):209–11.
14. Schrader KA, Nelson TN, De Luca A, et al. Multiple granular cell tumors are an associated feature of LEOPARD syndrome caused by mutation in PTPN11. *Clin Genet*. 2009 Feb;75(2):185–9.
15. Lohmann DR, Gillessen-Kaesbach G. Multiple subcutaneous granular-cell tumours in a patient with Noonan syndrome. *Clin Dysmorphol*. 2000 Oct;9(4):301–2.