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Granular cell tumor: importance of histopathology in determining malignant potential

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Abstract

Granular cell tumors (GCTs), sometimes called Abrikossoff tumors, are rare and typically benign soft tissue tumors. Malignant GCTs, which are even rarer than benign GCTs, can occur and must be detected early given their high mortality rate. Distinguishing between benign and malignant GCTs is difficult clinically; however, histologic evaluation plays an essential role in this endeavor.

Keywords: benign, excision, Fanburg-Smith criteria, granular cell tumor, malignant

Introduction

Granular cell tumors (GCTs) are rare mesenchymal soft tissue tumors that account for approximately 0.5% of all soft tissue tumors [1]. Granular cell tumors commonly present in middle-aged women as asymptomatic, slowly growing, solitary cutaneous, subcutaneous, or mucosal (particularly tongue) masses [1]; nearly 50% of all GCTs arise in the head and neck [2]. Although the histogenesis of GCT development remains unclear, it is hypothesized that these tumors arise from Schwann cells, as these tumors are positive for S100 and neuron-specific enolase [3]. Although most GCTs are benign, 0.5-2.0 % of cases can be malignant and have a poor prognosis [3].

On initial presentation, clinicians may not be able to distinguish between benign and malignant variants of GCTs. Clinically, malignant GCTs appear more commonly on the extremities and can affect the radial and sciatic nerve trunk [1]. Utilization of histopathologic criteria such as the Fanburg-Smith criteria can aid in differentiating benign and malignant GCTs. Early detection of GCTs and distinguishing benign from malignant variants is important, as malignant GCTs carry a 40% mortality rate and are associated with high rates of metastasis and recurrence [3]. The following case report describes an instance of a benign GCT manifesting in the scalp of an elderly woman.

Case Synopsis

A 65-year-old woman with no prior dermatologic disease presented to the dermatology clinic with a painful lesion on the right occipital scalp that had persisted for several months. Physical examination revealed a 1.1cm by 0.6cm skin-colored papule (**Figure 1**); on dermoscopy, comma-shaped vessels were observed.

A biopsy of the papule was performed. Histopathology revealed a benign appearing proliferation of epithelioid cells with a granular cytoplasm and pustulo-ovoid bodies present throughout (**Figure 2**); these findings were suggestive of a benign granular cell tumor. The patient was referred to a Mohs surgeon and the tumor was cleared in two stages, leaving a postoperative defect of 2cm by 1.8cm. Upon follow up three months after the excision no skin lesions were detected.

Figure 1. *Skin-colored papule overlying the right occipital scalp.*

Case Discussion

The differential diagnosis of GCT can be broad owing to a varied clinical presentation. Lesions can vary in size and morphology, presenting as smooth or rough, painful or painless papulonodules, from 0.2cm-10cm in size [4]. Based on the initial presentation of the patient's case, the differential diagnosis included neoplasms such as GCT, squamous cell carcinoma, glomus tumor, pilar cyst, follicular infundibular cyst (FIC), intradermal melanocytic nevus, and cutaneous metastasis from primary visceral malignancy [4]. Of these diagnoses, pilar cyst seemed most likely initially, as this is the most common cyst to appear in the scalp. Pilar cyst is derived from the outer root sheath of a hair follicle and is lined by squamous cells. Histologically, pilar cysts appear to have 3-4 layers of keratinocytes with abrupt keratinization into compact keratin and lack a granular cell layer [5]. Follicular infundibular cyst is a benign lesion believed to originate as a response to follicular occlusion related to an inflammatory process in the hair follicle resulting in infundibular epithelium hyperplasia [6,7]. Although these cysts commonly occur in the scalp, they are slow-growing and are more prevalent in males. Histologically FICs are lined by stratified squamous epithelium, contain a granular layer, and are filled with keratin debris [6,8]. Lastly, cutaneous metastasis from primary visceral malignancy, the most common of which is breast cancer, can present as nodules on the scalp, making it essential to biopsy any lesions of unclear etiology [9]. Given the rapid growth of this patient's mass, the patient's age and sex, as well as the

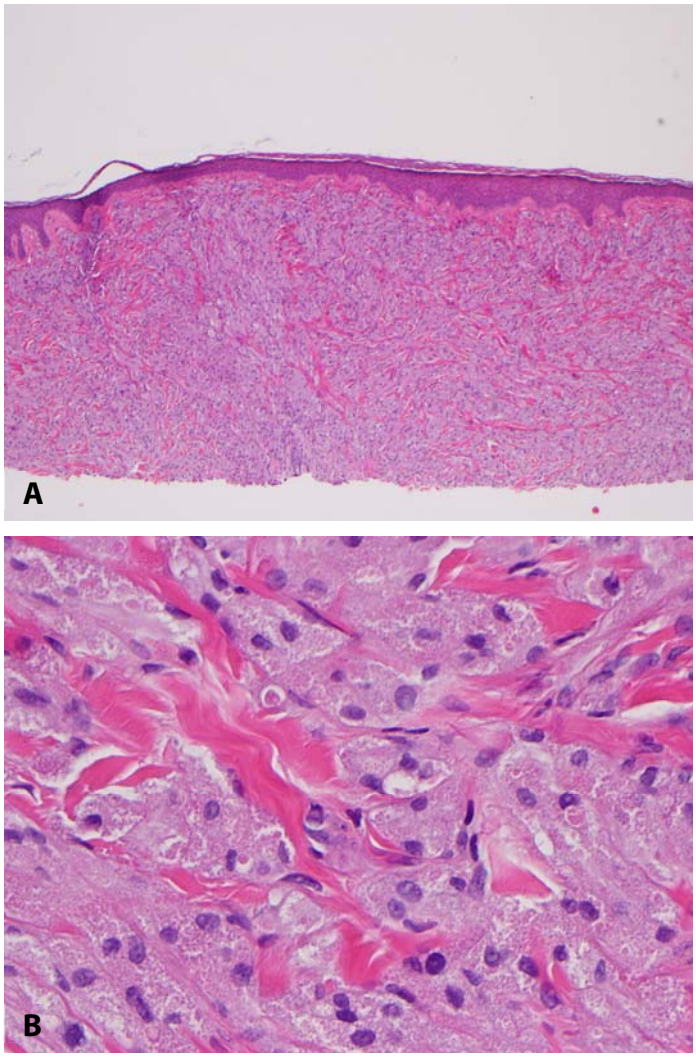

Figure 2. *H&E histopathology.* ***A)*** *Skin involved by granular cell tumor with nests of large cells with brightly eosinophilic granular cytoplasm, 40×.* ***B)*** *Granular cell tumor composed of ill-defined cells with uniformly small nuclei and occasional large granules surrounded by a clear halo (Pustulo-ovoid bodies of Milian), 400×.*

location of the papule, the diagnosis of GCT appeared most likely clinically and was confirmed on histopathology. Once GCT is suspected, determination of the malignant potential of the tumor is essential. Although only 0.5-2.0% of GCTs have been reported to be malignant, malignant GCTs have high rates of local recurrence and metastasis to regional lymph nodes, lungs, and bones [10]. Adverse prognostic factors include local recurrence, metastasis, larger tumor size, advanced age, presence of necrosis, increased mitotic activity, spindling of tumor cells, vesicular nuclei with large nucleoli, and Ki67 values greater than 10% [11]. A malignant GCT may be suspected clinically if the tumor demonstrates rapid regrowth, is greater than 4cm in size, or if evidence of distal metastasis exists [12].

Further evidence to support the malignant potential of a GCT can be found through histologic evaluation and utilization of the Fanburg-Smith criteria. The Fandburg-Smith criteria is comprised of 6 histologic criteria: necrosis, spindling of tumor cells, vesicular nuclei with large nucleoli, increased mitotic activity (> 2 mitoses/10 high-power fields at 200x magnification), high nuclear-to-cytoplasmic ratio, and pleomorphism. A tumor containing three or more of these features is characterized as histologically malignant. If one or two criteria are met, the lesion is considered atypical. Lesions that meet none of the criteria or solely demonstrate focal pleomorphism are considered histologically benign [11]. Benign GCTs are ill-defined lesions comprised of nests of large cells with eosinophilic, granular cytoplasm. The cell borders are often indistinct whereas the nuclei are uniformly small and round. Cells may contain large eosinophilic granules with surrounding clear halos, sometimes referred to as Putulo-ovoid bodies of Milian; these findings were observed on histopathology in this patient's case. Taken together, the benign findings on histopathology, the lesion's size, and its location on the scalp suggested the diagnosis of a benign tumor. [13].

Currently, the treatment of choice for benign or malignant GCTs is wide local excision. In the case of benign GCTs, this is primarily to prevent regrowth. For benign and atypical neoplasms, this treatment is considered curative. Malignant tumors require wide local excision in addition to adjuvant chemotherapy or radiotherapy. However, the utility of the adjuvant chemotherapy and radiotherapy remains unclear [3]. Furthermore, patients with GCT require follow-up to monitor for recurrence of the neoplasm or potential metastasis, though no guidelines exist currently to dictate follow-up frequency [3]. In a study by Singh et al. that analyzed cases of benign, atypical, and malignant GCTs upon excision and on follow-up for an average of 1.4 years, only the patient with malignant GCT presented with lung metastasis; this was detected at 3-month follow-up post excision [3]. This study highlights the importance of short-term follow up on patients with GCT as the malignant subtype can present with metastasis soon after excision.

Conclusion

Granular cell tumors disproportionately affect older women and can present as papulonodules of variable size on the head, neck, mucosal surfaces such as the tongue, or the extremities. Although nearly all GCTs are benign, malignant subtypes of GCTs have been reported and must be ruled out, as they are associated with greater mortality. For this reason, histologic evaluation is essential for diagnosis.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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