PATHOLOGICA 2021;113:131-135;
DOI: 10.32074/1591-951X-140

Case Report

Bilateral multifocal nodular oncocytic hyperplasia of the parotid gland: a rare entity

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Summary
Multifocal nodular oncocytic hyperplasia is an uncommon oncocytic lesion that rarely occurs in the parotid gland. Here, we report a case of a 43-years-old woman who presented with isolated gradual swelling in the 2 parotid regions. She underwent exofacial right parotidectomy. Histologic exam confirmed the diagnosis of oncocytoma arising in a background of multifocal nodular oncocytic hyperplasia with a histological variant of clear cells. Since the lesion was diagnosed as a benign lesion, surgery of the left side was not done. Our case is characterized by: early onset, the histological variant of clear cells and the presence of synchronous oncocytoma. We describe the clinical, histological and therapeutic features of this entity.

Key words: multifocal nodular oncocytic hyperplasia, parotid gland, oncocytoma, bilateral, histology

Received: May 22, 2020
Accepted: December 14, 2020

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Conflict of interest
The Authors declare no conflict of interest.

How to cite this article: Hammami B, Thabet W, Kellel R, et al. Bilateral multifocal nodular oncocytic hyperplasia of the parotid gland: a rare entity. Pathologica 2021:113:131-135. https://doi.org/10.32074/1591-951X-140

Introduction

Oncocytic lesions of the salivary glands are rare. The World Health Organization (WHO) classification of salivary oncocytic lesions includes: Oncocytosis, oncocytoma and oncocytic carcinoma. Multifocal nodular oncocytic hyperplasia (MNOH) or multifocal adenomatous oncocytic hyperplasia is an uncommon oncocytic lesion, which is a type of oncocytosis. It rarely occurs in the parotid gland. MNOH is a benign entity which is described as non-encapsulated nodules of oncocytic cells [1].
In this article, we report a new case of bilateral MNOH of the parotid gland and also describe the clinical, histological and therapeutic features of this entity.

Case report

A 43-year-old woman with no past medical history presented to our outpatient clinic with a 4-year history of a painless gradual swelling in the right parotid region. The swelling in the contralateral parotid region appeared about one year before the consultation and gradually increased in volume. There were no other complaints. Physical examination showed a firm, non-tender and well-limited bilateral parotid mass. The surfaces of the swellings were irregular (multiple nodules). They were not fixed to the underlying structures and the overlying skin was normal. The swellings

measured 4.5 x 3 cm on the right side and 3 x 2 cm on the left side. There were no signs of facial nerve involvement and no palpable cervical lymph nodes.
Pre-operative magnetic resonance imaging (MRI) showed bilateral multiple nodules in the parotid glands. The lesions were hypointense on T1 and T2-weighted sequences and hyperintense on diffusion-weighted images (Fig. 1). The apparent diffusion coefficient (ADC) value was low. Based on these characteristics, metastatic lymph nodes or lymphoma were suspected. Fine-needle aspiration (FNA) cytology from the right and the left masses revealed few small groups of oncocyte-like cells. Many salivary neoplastic and non-neoplastic lesions could be suspected: MNOH, oncocytoma, oncocytic carcinoma, Warthin tumour, salivary duct carcinoma, acinic cell carcinoma and oncocytic mucoepidermoid carcinoma.
In order to have a definitive diagnosis, the patient underwent right superficial parotidectomy. Intra-operative examination suggested a benign oncocytic tumour. Intra-operative examination of salivary gland specimens has several limitations: its accuracy in defining the histopathologic diagnosis is still in doubt. Significant effects of intraoperative frozen section complicate the interpretation of the excision tissue specimen. Freezing artifact significantly alters the histologic appearance of the cellular elements. In addition, because there are variations in cellular composition and architectural configurations in any single salivary gland tumour, it is often necessary to sample multiple areas.
There was no facial nerve palsy after the surgery or other complications.
Grossly, the surgical specimen measured 5 x 5 x 2 cm; the cut surface only revealed an encapsulated reddish-brown nodule which measured 2.7 cm (long axis). Microscopically, the nodule was surrounded by a definite capsule and the rest of the parotid parenchyma contained multiple non-encapsulated small nodules (Fig. 2). The nodule was formed of cells which were arranged in solid and trabecular patterns separated by a thin fibro-vascular stroma (Fig. 3). Tumour cells were large, with abundant clear cytoplasm and round regular nuclei with a single nucleolus (Fig. 4). The small nodules were composed of cells with the same characteristics as those described above. No histological signs of malignancy were found. The cells were positive for cytokeratin antibodies and for mitochondrial antibodies. These features were consistent with a diagnosis of oncocytoma arising in a background of multifocal nodular oncocytic hyperplasia with a histological variant of clear cells, of the parotid gland.
Since the lesion was diagnosed as benign process (hyperplasia), surgery of the left side was not done. The patient was regularly followed in our outpatient clinic. After 8 years of follow-up, the swelling in the left parotid region was slightly increased in volume and a 2 x 1 cm lump has reappeared on the other side (at 3 years postoperatively) whose size has remained stable (physical examination and MRI). Our attitude was to continue follow-up without surgical treatment.

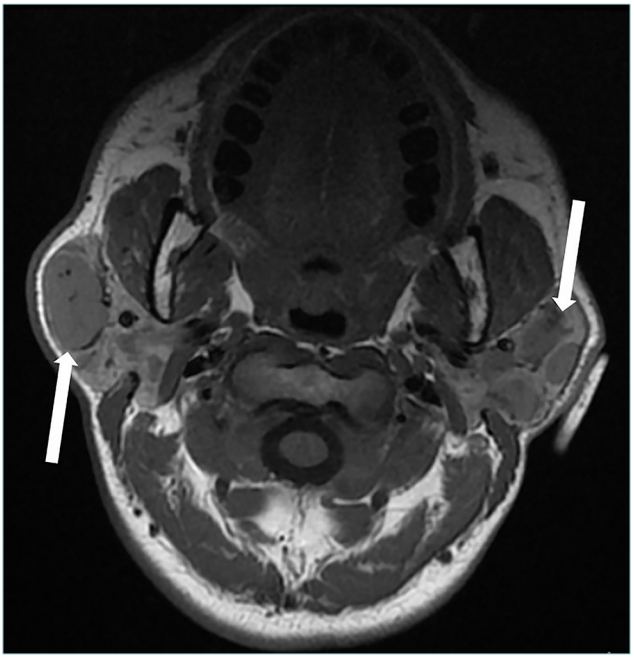

Figure 1. Preoperative MRI: axial T1-weighted image shows bilateral multiple hypointense nodules (white arrow) in the parotid glands.

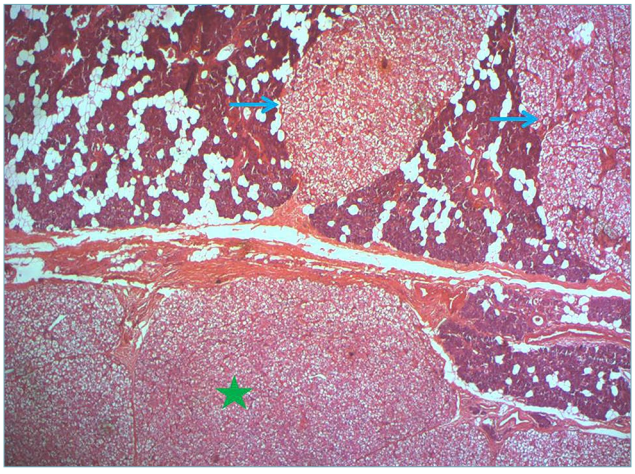

Figure 2. Encapsulated nodule (green star) with multinodular hyperplasia in the parotid parenchyma (blue arrow) (HEx 25).

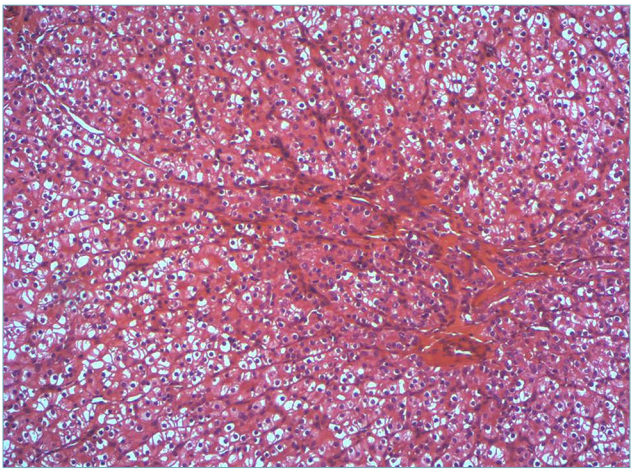

Figure 3. Cells arranged in solid and trabecular patterns separated by a thin stroma (HEx100).

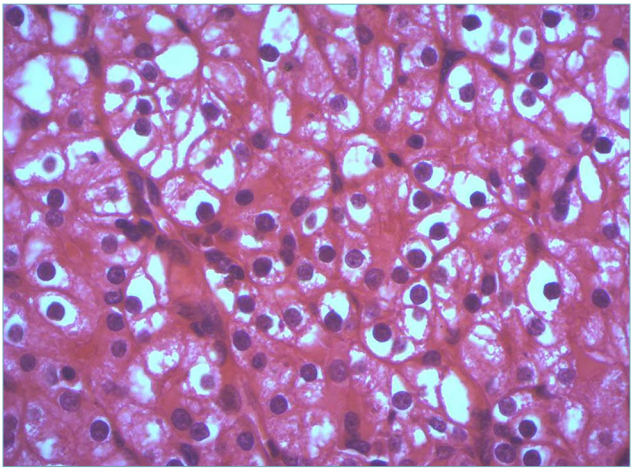

Figure 4. Large cells with abundant clear cytoplasm and round regular nuclei with a single nucleolus (HEx400).

Discussion

Bilateral and multifocal lesions of the parotid gland are unusual. Multifocal oncocytic lesions are more uncommon. Oncocytes are transformed epithelial cells which are characterized by an abundant eosinophilic granular cytoplasm (due to the increased numbers of mitochondria) and centrally located vesicular round nuclei typically with a single prominent nucleolus [1]. The appearance of these cells in the salivary glands is usually related to increasing age [2].

WHO classification of salivary gland neoplasms recognizes three oncocytic entities: Oncocytosis, oncocytoma and oncocytic carcinoma [3]. Oncocytosis is classified as diffuse hyperplastic oncocytosis and MNOH [3]. Diffuse hyperplastic oncocytosis is described as a non-encapsulated lesion with the entire gland replaced by oncocytic cells [3]. Oncocytosis makes up 0.1% of salivary gland lesions [4]. Oncocytic carcinoma is the malignant counterpart of oncocytoma (malignant appearing oncocytic cells).

MNOH is a very rare lesion of the parotid gland. It mostly affects women in the sixth decade [1]. It is characterized histologically by the presence of multiple non-encapsulated nodules of oncocytic cells, that are interspaced with normal tissue [1,4]. In our case, the nodules were mainly composed of clear cells. Clear cells also have abundant atypical mitochondria, but are characterized by glycogen accumulation and have no cytoplasmic structures in the central part of the cells [1,2]. In MNOH, clear cells are unusual [1]. The presence of clear cells can pose a diagnostic challenge with other clear cell neoplasms: clear cell mucoepidermoid carcinoma, clear cell adenocarcinoma, epithelial–myoepithelial carcinoma, clear cell acinic cell adenocarcinoma, clear cell myoepithelioma, and metastatic renal cell carcinoma [1]. In such a situation, special staining and immunohistochemistry are very helpful in assisting diagnosis [1]. Unlike MNOH, clear cell mucoepidermoid carcinoma, clear cell adenocarcinoma, epithelial-myoepithelial carcinoma, clear cell myoepithelioma and acinic cell adenocarcinoma are negative for glycogen and phosphotungstic acid hematoxylin (PTAH) [1]. Clear cell mucoepidermoid carcinoma is never completely composed of clear cells [1]. Epithelial-myoepithelial carcinoma is characterized by bicellular arrangement: ductal cells surrounded by clearly stained myoepithelial cells [1]. MNOH can also be distinguished from epithelial-myoepithelial carcinoma and clear cell myoepithelioma by using immunohistochemical myoepithelial markers: cytokeratin 5/6 (CK5/6), cytokeratin 14 (CK14), p63 protein, vimentin (VIM), α-smooth muscle actin (Alpha-SMA), calponin and S-100. Clear cell adenocarcinoma usually has a prominent hyalinized stroma [1]. Like MNOH, metastatic renal cell carcinoma contains glycogen and mitochondria, but cellular and nuclear pleomorphism, immunoreactivity for CD10, vimentin, and renal cell carcinoma antigen support the diagnosis of metastatic renal cell carcinoma [1].

Oncocytoma can arise in a background of MNOH, as in our case. Hyde et al. [2] also reported a case of bilateral parotid oncocytomas arising in a background of bilateral MNOH. It is not completely clear if the development of oncocytoma is a continuum of oncocytic hyperplasia or it is an independent event [2]. Hyde et al. [2] think that both scenarios may be in play, but more

research is certainly needed to clarify this point. Radiation exposure, metabolic mitochondrial defects and genetic predispositions are etiologic factors that may induce neoplastic change of oncocytic hyperplasia to oncocytoma [2]. Unlike MNOH, oncocytoma is characterized by the presence of a well-defined capsule that surrounds the tumour completely or at least partially [2]. MNOH may also be seen in combination with other benign or malignant salivary gland tumours, particularly pleomorphic adenoma [1].

The pathogenesis of this condition is unclear, but mitochondrial dysfunction and defective cellular metabolism (responsible for mitochondrial hyperplasia and pleomorphism) have been suggested [4].

Cytologic findings in FNA of MNOH cases are not well characterized, limiting preoperative identification [5]. Moreover, cytologic findings overlap with those of many benign and malignant parotid conditions that enter the differential diagnosis of MNOH, including Warthin tumour, oncocytoma, papillary oncocytic cystadenoma/cystadenocarcinoma, salivary duct carcinoma, acinic cell carcinoma, mammary analog secretory carcinoma (MASC), and oncocytic mucoepidermoid carcinoma (oncocytic cells can be observed in these tumours) [5].

Cytologically, the differential diagnosis between MNOH and other benign oncocytic salivary lesions is more difficult than malignant tumours [5]. The oncocytic cells in Warthin tumour demonstrate bilayered architecture, and they are accompanied by prominent lymphocytes with lymphoid tangles and a background of granular proteinaceous debris [5]. FNA specimens from oncocytomas are characterized by higher cellularity and a prominent population of single cells as well as tissue fragments [5]. More complex papillary architecture and psammoma bodies are in favor of papillary oncocytic cystadenoma [5].

Salivary duct carcinoma, the archetypal malignant oncocytic neoplasm, is characterized by the cribriform to papillary architecture, marked nuclear pleomorphism, and necrotic background [5]. MNOH lacks the basophilic cytoplasmic granules, cytoplasmic vacuolation, and background naked nuclei characteristic of acinic cell carcinoma [5]. Additionally, MNOH does not demonstrate the true papillary architecture, abundant vacuolated cytoplasm, and secretory material observed in MASC [5]. Unlike MNOH, mucoepidermoid carcinoma is cytologically characterized by the true mucin-containing cells and intermediate cells [5].

Thus, the gold standard for precise diagnosis is histological exam [3,4]. Nevertheless, MNOH should be considered in the differential diagnosis of oncocytic neoplasms on FNA cytology especially when it shows a paucicellular specimen composed of small groups of oncocytic cells and even can favour it in elderly patients with multiple nodules [5].

The diagnosis of MNOH should be considered when CT (computed tomography) or MR imaging shows multiple nodules in the parotid gland.

The progression of MNOH is very slow [4].

MNOH is widely accepted to be a nonneoplastic benign process with no risk of malignant transformation [5].

For some authors [4], total surgical excision (total parotidectomy) is the treatment of choice. For others [1,5], total surgical resection is not necessary, in the absence of functional or cosmetic considerations, since MNOH is a benign lesion and has no potential for malignant transformation.

In our case, the patient underwent right superficial parotidectomy. Due to the benign nature of MNOH with no risk of malignant transformation, the removal of the deep lobe of the right parotid gland as well as the left parotid gland, was not done. In addition, we decided not to treat the left side, since the patient had not cosmetic or functional complaints at the time of diagnosis and during follow-up. Therefore, based on our reported case, we believe that total surgical resection is not necessary.

Recurrences can be seen after incomplete resection. Akbulut et al. [4] reported a case of metachronous MNOH (the bilateralism of the lesion appeared 10 years later), so they recommend the follow-up of unilateral MNOH cases.

Conclusion

Unlike classic MNOH, our case is characterized by: the early onset, the histological variant of clear cells and the presence of synchronous oncocytoma. Although MNOH is an infrequent entity, it should be considered in case of multinodular lesion of the parotid gland. Oncocytic lesions of salivary gland can pose considerable difficulty to the cytopathologist, and a histopathological examination often remains the cornerstone of diagnosis [3]. Many parotid conditions can enter the differential diagnosis of MNOH especially clear cell neoplasms. MNOH has no potential for malignant transformation.

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