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CASE REPORT

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Palatine tonsil metastasis of cecal mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN): A unique case

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Abstract

This case demonstrates the importance of understanding that patients with malignant neoplasms may exhibit metastases in unexpected sites and illustrates the necessity of a thorough clinical examination and pathologic correlation.

KEYWORDS

colon, metastasis, neuroendocrine tumors, tonsil, tonsillar neoplasms

1 | INTRODUCTION

A 68-year-old male with a history of previously operated right colonic mixed neuroendocrine-non-neuroendocrine neoplasm (MINEN) presented with a swelling of the left palatine tonsil. Tonsillectomy was performed, and histology showed a tumor with features of MINEN, the first ever reported such tumor with metastasis to the tonsils.

Metastases constitute <1% of tonsillar neoplasms[1] with breast and lung carcinomas, as well as malignant melanoma, being the most frequent primary sites.[2] Tonsillar metastases of colorectal adenocarcinoma are rare; only 13 cases have so far been reported,[3] among which five concern a signet-ring cell type.[2,4] On the other hand, small cell carcinoma is the most frequent type among the very few reports of tonsillar metastases of neuroendocrine tumors,[1,5] of which only a handful of cases have so far been reported.[6,7] When a diagnosis of a neuroendocrine neoplasm is established at the head and neck region, imaging is necessary to exclude possible metastases, since they occur more frequently in other body regions.[8]

We herewith report a case of a cecal mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) metastatic to the left palatine tonsil, this being, to our best knowledge, the first such case ever reported.

Tsakiraki and Delides equal contribution.

2 | CASE REPORT

A 68-year-old Caucasian male was referred to the ENT department of our hospital because of a left palatine tonsillar mass and odynophagia. Physical examination revealed an ulcerated area on the upper pole of the enlarged tonsil with no other remarkable findings. An MRI scan (Figure 1) confirmed the left tonsillar enlargement with paramagnetic enhancement.

His past medical history included a right hemicolectomy, 6 months earlier, due to an 8cm large, mainly cecal mixed adenoneuroendocrine carcinoma (MANEC), according to the former WHO. classification,[9] or a mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), according to the current WHO classification. The carcinoma was extending to the base of the appendix vermiformis (its tip uninvolved) and infiltrating an adjacent ileal loop. The tumor consisted of two components: a poorly differentiated adenocarcinoma with signet-ring-like cells containing Alcian blue-positive mucin, either diffusely arranged or floating within pools of mucin (approximately 70% of the tumor), and a neuroendocrine carcinoma with rosette formation (30% of the tumor). Both components were decorated with immunostains against chromogranin A and synaptophysin; moreover, signet-ring-like cells were immunopositive for CK20. Proliferation rate, assessed by Ki67 immunostain, amounted to 70% in some areas. The tumor infiltrated 19 out of 22 retrieved colonic lymph nodes. A full-body computed tomography (CT) revealed no distant metastases. Following excision, the patient was treated with chemotherapy with six cycles of adjuvant FOLFOX through a central catheter, which was administered uneventfully. FOLFOX is a combination of IV Oxaliplatin, IV Leucovorin, IV Fluorouracil, initially IV bolus followed by IV continuous 44 h infusion, repeated every 14 days. This represents the standard adjuvant chemotherapy for stage III colon cancer. While on chemotherapy, he developed the tonsillar mass and was referred accordingly. A radical left tonsillectomy was consequently performed.

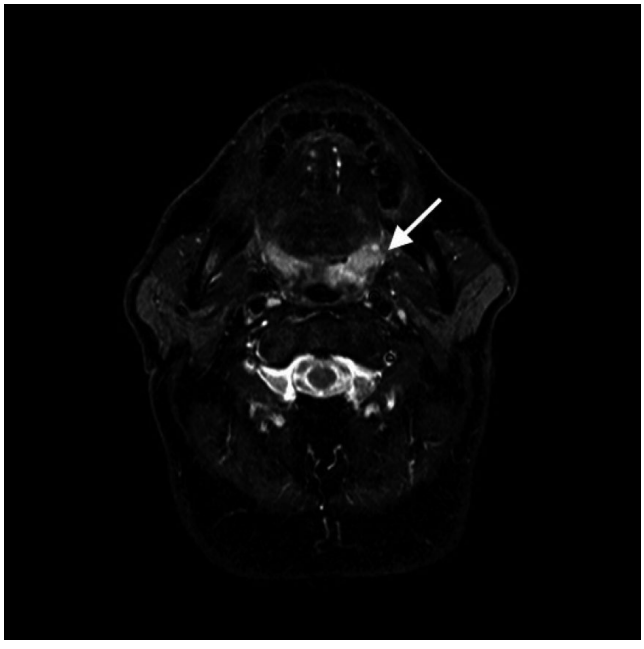

FIGURE 1 Imaging findings. MRI scan of the neck, showing (arrow) an enlargement of the left palatine tonsil with paramagnetic enhancement

Microscopic examination of the specimen disclosed a 2.7 cm large, ulcerated, poorly differentiated carcinoma containing many signet-ring-like cells also filled with Alcian blue-positive mucin (Figure 2). Many tumor cells were positive for CKAE1/AE3 (some in a "dot-like" pattern, suggestive of neuroendocrine differentiation) and synaptophysin, whereas a few were immunostained for CK20 as well (Figure 3). This was therefore considered as a tonsillar secondary of the previously diagnosed mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN).

Immunohistochemical expression of DNA mismatch repair (MMR) proteins was investigated, showing concomitant loss of MLH1 and PMS2 proteins, suggestive of microsatellite instability (Figure 3). Moreover, analysis of KRAS, NRAS, and BRAF gene status identified a Val600Glu mutation of the BRAF gene.

Following the completion of 6 cycles of FOLFOX, a scheduled restaging demonstrated unequivocal systemic progression of the disease. He was thus scheduled for salvage chemotherapy with 6 cycles of Cisplatin/Etoposide with partial response.

3 | DISCUSSION

According to the former WHO. classification,[9] tumors with the above-mentioned characteristics were first defined in 2010 as mixed adenoneuroendocrine carcinoma (MANEC): They consist of both an epithelial (adenocarcinomatous) and a neuroendocrine malignant component, a percentage of at least 30% required for each component.[9,10] The new (2017) WHO Classification of Tumors of the Digestive System replaces the term MANEC with a new entity, named mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN),[11] of which three types are recognized: collision (two separate, non-intermixed components), composite (two separate, focally intermixed components), and a rare amphicrine (one component displaying features of both adenocarcinomatous and neuroendocrine differentiation). Our case fits to the composite type.

The majority of MiNENs arise from the appendix,[12] but tumors have also been described in other locations, for example, pancreas, gallbladder, stomach.[13] Colonic MiNENs are extremely rare, mainly reported as case reports[14–17]; our case is, up to now, the eighth located at the cecum.[15]

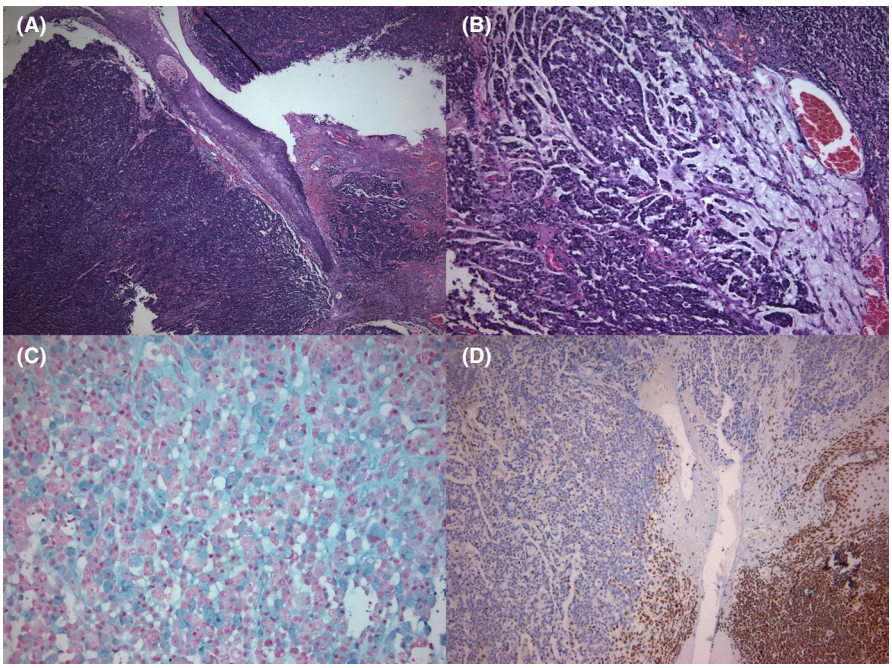

FIGURE 2 Histology, histochemical and immunohistochemical study of the tumor. (A) MINEN invades the tonsillar squamous epithelium provoking ulceration. H&E ×4. (B) Signet-ring-like cells floating within pools of mucin. H&E ×10. (C) Many signet-ring-like cells filled with Alcian blue-positive mucin. Alcian-Blue ×20. (D) Concomitant loss of PMS2 (positive lymphocytes as witness at the right side) and MLH1 (not shown here) proteins, suggestive of microsatellite instability. PMS2 ×10

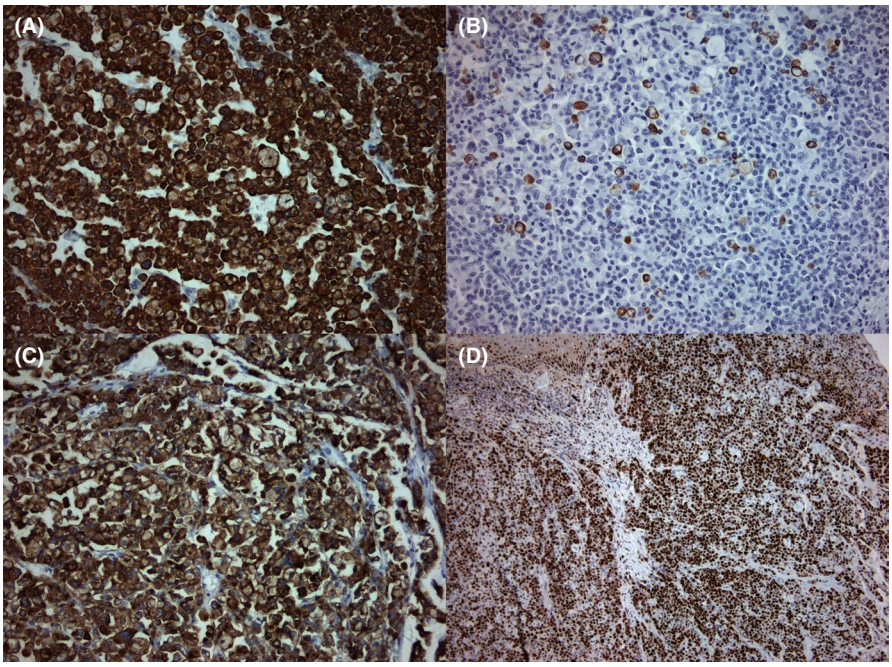

FIGURE 3 Immunohistochemical study of the tumor. (A) Tumor cells are positive for CKAE1/AE3 (some in a "dot-like" pattern, suggestive of neuroendocrine differentiation. Signet- ring cells are also evident. CKAE1/3 ×20. (B) CK20 positive signet-ring cells. CK20 ×20. (C) Synaptophisin stains not only the neuroendocrine cells but also the signet ring cells of the neoplasms indicating an amphicrine nature. Synaptophysin ×20. (D) The proliferation index was approximately 70%. Ki-67 ×10

Mixed neuroendocrine-non-neuroendocrine neoplasms are highly aggressive, with a significant proportion of patients presenting with advanced stage disease, especially when the primary is located in the appendix.[18] Each component can metastasize separately, regardless of its percentage in the primary tumor.[19] More specifically, colonic MiNENs usually present at an advanced stage, both with nodal and distant metastases, the liver being the site most frequently involved.[20,21] Tumors containing signet-ring-like cells seem to fare better than those lacking these cells.[12] BRAF mutations seem to be more common in colonic MiNENs compared to conventional colorectal adenocarcinomas[12,22]; moreover, these tumors seem to harbor microsatellite instability, especially concerning MLH1 and PMS2 proteins[23]; it is to be noted that both features were present in our case. The presence of BRAF V600E mutation is associated with aggressive clinical course with early metastasis in unusual metastatic sites. The early development of a palatine metastasis in this patient could be associated with the presence of the BRAF mutation.[24]

Metastases to the oral cavity or oropharynx are rare, comprising only 1–3% of all oral–oropharyngeal neoplasms. Specifically, tonsillar secondaries from non-hematological malignancies account for only 0.8% of all tonsillar malignancies.[25] Only thirteen cases of colonic primaries with tonsillar metastases have so far been reported,[2,3,26] among which

five concerned tumors with a signet-ring-like component, but none was a MANEC/MiNEN, our case being therefore, to our best knowledge, the first ever described.

A palatine metastasis presents with common symptoms such as odynophagia, dysphagia, tonsillitis, or visible swelling and may delay definite diagnosis. Tonsillar involvement may even present before the diagnosis of the primary site.

The pathophysiological mechanism of spread from a colonic primary remains a moot point, considering that palatine tonsils, unlike lymph nodes, lack afferent lymphatic vessels. Theories so far formulated include both lymphogenous (via retrograde cervical lymphatic circulation and through the thoracic duct[27]) and hematogenous (either through the systematic arterial blood flow passing through the lungs or through Bateson's plexus[28]) routes.

Prognosis of patients with tonsillar metastases is no more than 9 months, regardless of the histology of the primary tumor.[29] Generally, patients with gastrointestinal MiNENs appear to have a better overall survival than patients with pure NECs and this is mainly because of more advanced stage at the time of diagnosis of the latter.[30] MiNENs can be stratified in different prognostic categories, according to the grade of malignancy of each component (high-grade malignant and intermediate),[31] but what mainly counts for the prognosis of high-grade malignant MiNENs is the stage of the disease.

Furthermore, the molecular classification of colon cancer has provided significant information which separates different subpopulations with different clinical course and individualized decision on treatment selection. Following sequential trials of BRAF targeting in these patients, a positive randomized phase III trial of the combination of Encorafenib, Binimetinib, and Cetuximab improved progression-free survival vs. standard chemotherapy and this represents the current standard of care in second-line therapy. When our patient was treated, this combination was experimental and not available. As of today, for a patient with a metastatic neuroendocrine colon adenocarcinoma carrying the BRAF V600E mutation the combination of targeted agents and the Cisplatin/Etoposide regimen would represent alternative options for systemic therapy.[24]

Immunohistochemistry remains a useful and indispensable tool for the investigation of unknown primary site carcinomas as well as for the establishment of diagnosis and confirmation of metastasis with a known history. In general, a primary useful algorithm of antibody's combination is Cytokeratin 7 (CK7) and Cytokeratin 20 (CK20), and subsequently, a panel of organ-specific markers such as CDX2, TTF-1, GCDFP-15 is judicious to be stained, in concordance always with the hematoxylin and eosin initial approach.[32] Specifically, in this case the neuroendocrine nature of the tumor was evident, so a panel of neuroendocrine markers (chromogranin, synaptophysin, CD56) is recommended.[33]

4 | CONCLUSION

Our case constitutes the first ever reported concerning palatine tonsillar metastasis of a MiNEN. Clearly, it demonstrates the importance of understanding that patients with malignant neoplasms, especially with end-stage disease, may exhibit metastases not always at expected sites and of course it illustrates the necessity of a thorough clinical examination and pathologic correlation. A diagnostic tonsillectomy should always be performed in patients with such tumors when a clinical impression of an unresolved tonsillar swelling or inflammation is evident.

CONFLICTS OF INTERESTS

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION

Alexander Delides and Zoi Tsakiraki: involved in conceptualization, methodology, and writing. Vasileia Damaskou: involved in data curation and editing. Sofia Psarogiorgou, Evangelos Giotakis, and lias Athanasiadis: involved in data curation. Aris Spathis: involved in review and editing. Ioannis G. Panayiotides: involved in supervision, review, and editing.

CONSENT STATEMENT

Written informed consent was obtained from the patient for the publication of this case report.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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