Neuroendocrine Cancer of the Lung: A Diagnostic Puzzle

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ABSTRACT

Here we report the case of a pulmonary neuroendocrine tumor (pNET) in which the pathological diagnosis was revised several times over the course of the patient's disease because of atypical behavior of the tumor; consequently, the patient was treated with various treatment schedules.

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Case Report

A 51-year-old female former smoker was referred to our academic hospital with a metastasis of a poorly differentiated carcinoma in a subcutaneous lesion on the posterior thoracic wall (Figs. 1*A–E*; Table 1, report I). Revision of the initial biopsy and a new fine-needle aspiration biopsy of an additional subcutaneous mass in the breast revealed a non–small cell lung carcinoma with preference for a large cell neuroendocrine carcinoma (LCNEC) and mitotic index of 19 in 10 high-power fields (HPFs) that most likely originated from the lung (Table 1, reports II and III). Both an ^{18}F-fluorodeoxyglucose–positron emission tomography scan and a ^{68}Ga-DOTATATE positron emission tomography/computed tomography scan showed multiple nodules in the right upper and lower lobe as well as subcutaneous and liver metastases. Stage IV LCNEC was diagnosed, and the patient was enrolled in a clinical trial with paclitaxel-carboplatin and bevacizumab with the addition of a nitroglycerine patch (Paclitaxel-Carboplatin-Bevacizumab ± Nitroglycerin in Metastatic Non-Squamous-Non–Small Cell Lung Cancer, NCT01171170). After the patient's disease had remained stable and her clinical condition had remained good for 12 months, new subcutaneous lesions developed on her scalp and thorax. A surgical biopsy of one of the scalp lesions was performed, and the pathologist diagnosed a combined large cell and small cell neuroendocrine carcinoma (Table 1, report IVa; Figs. 1*F–J*). Carboplatin-etoposide chemotherapy was subsequently initiated; however, the scalp metastases showed no response.

After discussion in a multidisciplinary team, all the biopsy findings were revised and the tumor was reclassified as an atypical carcinoid with a mitotic index of 6/10 (HPFs). This reclassification was supported by the results of an additional KI-67 stain (15%–20%) (Table 1, report IVb). Peptide receptor radionuclide therapy with octreotide was administered, but because of side effects, it was halted at the patient's request.

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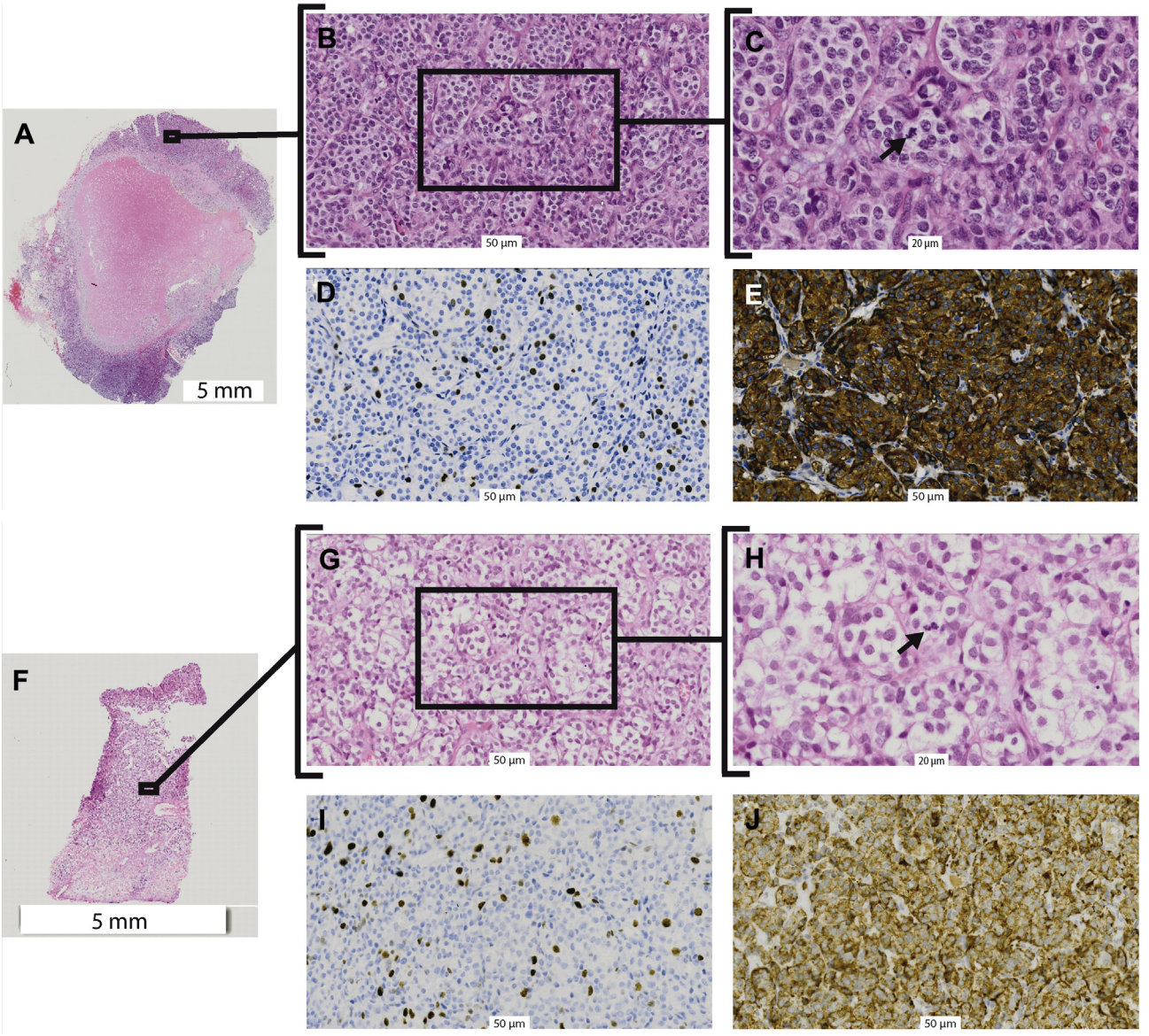

Figure 1. Pathological slide overview of the subcutaneous posterior thoracic wall lesion and scalp lesion from the same patient that was, after multiple revisions, classified as atypical carcinoid. Posterior thoracic wall biopsy: (*A*) Overview slide showing the tumor with central necrosis. (*B*) Organoid growth pattern with nests of large cells containing abundant cytoplasm and monotonous nuclei; no dotlike necrosis (magnification ×20). (*C*) Single mitosis in the center (*arrow head*) (magnification ×40). (*D*/*E*) Positive immunohistochemical staining for Ki-67 and chromogranin-A. Subcutaneous scalp biopsy: (*F*) Overview slide on which slight crush artefacts are observed in the left top in a possibly less well preserved biopsy. (*G*) Slightly more diffuse pattern with occasional nests, showing large cells with abundant clear cytoplasm and nucleoli. No presence of necrosis (magnification ×20). (*H*) Single mitosis in the center (*arrow head*) (magnification ×40). (*I*/*J*) Positive immunohistochemical staining for Ki-67 and chromogranin-A.

Eventually, the patient was referred for participation in a randomized phase 2 trial for atypical carcinoid (Three-Arm Trial to Evaluate Pasireotide LAR/Everolimus Alone/in Combination in Patients with Lung/Thymus NET [NCT01563354]) and was assigned to treatment with the mammalian target of rapamycin inhibitor everolimus. Currently, the patient is in a good clinical condition and her disease is stable 14 months after initiation of everolimus and 42 months after the initial diagnosis.

Because of the unusual clinical development of this case and the difficulty in reaching a histological diagnosis, we requested that three expert pathologists perform a blind revision of the two histological specimens. They were unaware of the fact that the specimens belonged to one and the same patient and did not know the location of the primary tumor. Two pathologists (B and C) diagnosed atypical carcinoid/neuroendocrine tumor grade 1–2 in both the initial biopsy sample and

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