Dear Editors,

Pigmented epithelioid melanocytoma (PEM) is considered a low-grade variant of malignant melanoma that is frequently accompanied by lymph node metastases [1]. Five PEM cases with distant metastases and two lethal cases have been reported. Pigmented epithelioid melanocytoma occur more frequently in children and young adults, but have been reported in all age groups [1]. The lesions occur on the trunk, extremities, head and neck as well as on the conjunctiva [2]. Dermatoscopic features include homogenous black, blue and brown pigment, comedo-like openings, crystalline structures and pigmentation extending into satellite lesions and lymphatic vessels. Histopathology reveals a dermal proliferation of pigmented dendritic and epithelioid melanocytes with larger, less pigmented epithelioid cells [3].

Case Report

A 7-year-old female patient presented with a pigmented nodule above the left mandible, measuring 6 mm in diameter (Figure 1a). The lesion had been apparent for about eight months and was growing in size. Dermatoscopy showed homogenous black and blue pigment with few linear peripheral extensions of pigmentation. Three barely noticeable hyperpigmentations in the periphery of the tumor were suggestive of satellite lesions (Figure 1b). Wide local excision revealed an asymmetric lesion with pleomorphic, mostly epithelioid, melanocytic cells. Enlarged melanocytes with prominent nucleoli were located within lymphatic vessels, no necrosis was evident. In immunohistochemical examination the tumor cells were positive for MelanA, HMB-45, SOX10 and S-100 (Figure 2). Phosphohistone H3 (PHH3) did not reveal...
malignancy. After detailed discussion of the histologic findings and presence of satellite lesions with the patient and her parents, sentinel lymph node biopsy (SNLB) was performed. Tumor deposits were detected in one of three lymph nodes, without signs of capsular invasion. This case was discussed in our interdisciplinary tumor board, and an off-label adjuvant anti-programmed cell death protein 1 (PD-1) monotherapy with pembrolizumab 2 mg/kg bodyweight every three weeks for one year was offered, despite potential side effects [4]. Thus far, the patient has received the first five doses and has tolerated the therapy well. Follow-up stagings have been unremarkable.

Discussion

Pigmented epithelioid melanocytoma frequently show regional lymph node metastases (46 % of cases with positive sentinel lymph node biopsy [SLNB]), but patients still demonstrate an overall favorable clinical course with rare occurrences of distant metastases [1]. The largest cohort of patients with PEM shows only 22.4 % of patients with lymph node involvement. However, the analysis of lymph node involvement in patients of the same cohort who underwent SLNB showed a positive rate of 43.8 % [5]. This discrepancy could support SLNB as a diagnostic approach. Neither wide local excision nor SLNB are considered standard. Lymphadenectomy has been suggested in PEM patients with positive SLN [6, 7]. A retrospective study presented long-term follow up of 26 patients with a median follow-up period of 67 months, in which all patients were free of disease, allowing PEM to be regarded as a low-grade melanocytic tumor [1, 7, 8]. Treatment with interferon has been reported in five cases [1, 6]. In other cases, close clinical follow-up was performed.

Major histological differential diagnoses of PEM include atypical deep penetrating nevus, malignant blue nevus and pigment-synthesizing melanoma. In the present case the typical architectural features of a deep penetrating nevus with deep periadnexal and perivascular extension into the subcutaneous tissue were not present. However, as distinguishing these entities histopathologically is challenging, we applied further genomic analyses to reach a diagnosis. Pigmented epithelioid melanocytoma, when compared to melanoma, harbors different genetic alterations without a set of distinct alterations. A definition of PEM as “pure” or “combined” in regard to their distinct genetic alterations has been proposed. Pigmented epithelioid melanocytoma that are considered to be combined (features of both common nevus and PEM), show alterations in BRAF and PRKAR1A genes, whereas pure PEM show alterations in MAP2K1, PRKAR1A and reveal PRKCA fusions [8]. In our patient, neither genetic alterations of pure or combined PEM, nor alterations typical of a Spitz nevus, blue nevus or deep penetrating nevus have been detected. The alterations we identified affected NOTCH1, NOTCH2, NOTCH4, SPEN, and HERC2. Known to play a role in tumorigenesis of different tumors, NOTCH alterations have not been described in PEM previously [9]. Although genomic analyses may be beneficial for diagnosis and treatment choice for skin tumors [10, 11], histology remains the critical diagnostic element in this case, where PEM was diagnosed by a number of highly experienced dermatopathologists.

This case underlines the diagnostic relevance of SLNB in PEM, which we propose as a diagnostic standard.

Conflict of interest

S.U. declares personal fees and non-financial support from: Bristol Myers Squibb; personal fees and other: Merck Serono, Merck Sharp & Dohme, Novartis, Roche; outside the submitted work. E.L. reports personal fees and other from Roche, Bristol-Meyers-Squibb, Novartis, Sanofi, MSD; other from: Actelion, Amgen, Pierre Fabre, SunPharma, Boehringer-Ingelheim, medac; outside the submitted work. L.Z. reports personal fees and other from: Bristol-Meyers-Squibb,

Table 1 Summary of genetic alterations identified in this PEM. Analysis of the tumor tissue revealed wild-type sequences for common mutations in melanoma. Other genetic alterations remain without clear functional significance.

| GNAQ | GNA11 | PRKCA | BRAF | NRAS | NF1 | cKIT | TERTprom | PD-L1 | NOTCH1 | NOTCH2 | NOTCH4 | SPEN | HERC2 |
|------|-------|-------|------|------|-----|------|---------|-------|--------|--------|--------|------|-------|
| wt   | wt    | wt    | wt   | wt   | wt   | wt   | wt       | Negative (0 %) | T1402A | A217T; P66S | L16del | L326fs; L3270fs | T566M |

Abbr.: wt, wild type.
Correspondence  Clinical Letter

MSD, Pierre Fabre, Roche, Novartis; other from: Sanofi, Amgen; outside the submitted work. D.S. reports personal fees and non-financial support from: Roche/Genentech, Merck Serono, Sanofi/Regeneron, Amgen; grants, personal fees, non-financial support and other from: BMS, Novartis; personal fees from: Merck Sharp & Dohme, Immunocore, Incyte, 4SC, Pierre Fabre, Array BioPharma, Pfizer, Philogen, Regeneron, Nektar, Sandoz; outside the submitted work. All other authors declare no conflict of interest.

Carl Maximilian Thielmann1, Selma Ugurel1, Elisabeth Livingstone1, Lisa Zimmer1, Bruno E. Paredes2, Thomas Brinkmeier3, Klaus Griewank1, Dirk Schadendorf1, Joachim Klode1, Ingo Stoffels1, Eva Hadaschik1

(1) Department of Dermatology, Venereology and Allergology, University Hospital Essen, University School of Medicine Duisburg-Essen, Essen, Germany
(2) Dermatopathologie Friedrichshafen, Friedrichshafen, Germany
(3) Hautärzte am Markt, Dortmund, Germany

Correspondence to
Carl Maximilian Thielmann, MD
Department of Dermatology, Venereology and Allergology
University Hospital Essen
Hufelandstrasse 55
45147 Essen, Germany
E-mail: carlmaximilian.thielmann@uk-essen.de

References
1. Zembowicz A, Carney JA, Mihm MC. Pigmented epithelioid melanocytoma: a low-grade melanocytic tumor with metastatic potential indistinguishable from animal-type melanoma and epithelioid blue nevus. Am J Surg Pathol 2004; 28(6): 31–40.
2. Bissig A, Moulin A, Spahn B et al. Conjunctival pigmented epithelioid melanocytoma: a clinicopathological case report. Arch Ophthalmol 2012; 130(11): 1478–9.
3. Moscarella E, Ricci R, Argenziano G et al. Pigmented epithelioid melanocytoma: clinical, dermoscopic and histopathological features. Br J Dermatol 2016; 174(5): 1115–7.
4. Reschke R, Jaeger I, Mehnert-Theuerkauf A, Ziener M. Therapeutic understanding and health related quality of life in stage III/IV melanoma patients treated with novel adjuvant therapies. J Dtsch Dermatol Ges 2021; 19(2): 215–21.
5. Cheng PS, Chuang SS, Kuo TT, Lai FJ. Pigmented epithelioid melanocytoma: Report of a case and review of 173 cases in the literature. Dermatologica Sinica 2012; 30(2): 57–64.
6. Bax MJ, Brown MD, Rothberg PG et al. Pigmented epithelioid melanocytoma (animal-type melanoma): An institutional experience. J Am Acad Dermatol 2017; 77(2): 328–32.
7. Mandal RV, Murali R, Lundquist KF et al. Pigmented epithelioid melanocytoma: favorable outcome after 5-year follow-up. Am J Surg Pathol 2009; 33(12): 1778–82.
8. Cohen JN, Joseph NM, North JP et al. Genomic analysis of pigmented epithelioid melanocytomas reveals recurrent alterations in PRKAR1A, and PRKCA genes. Am J Surg Pathol 2017; 41(10): 1333–46.
9. Hu B, Castillo E, Harewood L et al. Multifocal epithelial tumors and field cancerization from loss of mesenchymal CSL signaling. Cell 2012; 149(6): 1207–20.
10. Kutzner H, Jutzi TB, Krahl D et al. Overdiagnosis of melanoma – causes, consequences and solutions. J Dtsch Dermatol Ges 2020; 18(12): 1336–43.
11. Forschner A, Forchhammer S, Bonzeim I. NTRK gene fusions in melanoma: detection, prevalence and potential therapeutic implications. J Dtsch Dermatol Ges 2020; 18(12): 1387–92.