Eruptive melanocytic nevi with malignant transformations and the connection to BRAF and p16 mutations

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Abstract

Eruptive melanocytic nevi (EMN) is a rare phenomenon with an unclear pathogenesis. Mutation on a molecular basis has been proposed, but insufficient data are available to confirm this hypothesis. Theoretically, the possibility of malignant transformation is high, but no previous definite cases had been reported. Herein, we report the first case of a patient with EMN in whom hypopharyngeal low-grade melanocytic malignancies were detected using a fibrolaryngoscope. BRAF activation and p16 mutations were discovered through real-time polymerase chain reaction and immunohistochemical staining on EMN tissue samples, respectively. The significance of these findings has yet to be determined.
predominantly epithelioid nevus cells with prominent central eosinophilic nucleoli, focal hyperchromatism and mild nuclear atypia (Figure 2B–D). The lesion revealed both benign characteristics, including a well-circumscribed architecture with maturation and no mitotic activity, and troubling characteristics, including a slightly asymmetrical architecture, confluent cell nests, and frequent pagetoid extensions of the nevus cell into the surface epithelium, even in the upper half of the epithelium. These histologic features led to a diagnosis of melanocytic tumor with uncertain malignant potential (MELTUMP). After 1 month, the patient returned for follow-up. The number of skin lesions had increased and some of them had become more raised and enlarged. He received a fibrolaryngoscopy again, and three newly erupted pigmented nevi were detected over the hypopharynx. We detected BRAF V600E mutations by using a real-time melting curve analysis of PCR on four of the excised tissues and using IHC to identify p16 in five of the excised tissues. The PCR

Figure 1 (A) Numerous erupted melanocytic nevi in a 32-year-old man. (B) Close-up view of abdominal region. Nevi are 1–4 mm in diameter, mildly dome-shaped, and blackish. (C) Microscopically, the lesion demonstrates features of a Spitz nevus, including a compound structure with a well-circumscribed outline, and heavy pigmentation (hematoxylin and eosin 40×). (D) High-power view showing large epithelioid and spindle nevus cell aggregation. (hematoxylin and eosin 100×).

Figure 2 (A) A pigmented lesion detected under a fibrolaryngoscope over the hypopharynx. Three newly erupted pigmented lesions are detected 1 month later in the same region (not shown). (B) Histologic examination of the hypopharyngeal lesion reveals well-demarcated but slightly asymmetrical proliferation with heavy pigmentation under the scanning view (hematoxylin and eosin 40×). (C) Frequent pagetoid spread of nevus cells, singly and in nests are noted, they even located in the upper half of the epithelium (hematoxylin and eosin 200×). (D) Close-up view: the lesion is composed of confluent large epithelioid nevus cells. The cells show mild pleomorphism and nuclear atypia. No mitotic figures or atypical mitosis are detected throughout the lesion (hematoxylin and eosin 400×).
result indicated the presence of BRAF V600E mutations in three of the four excised tissues (Supplementary Table 1). The IHC staining for the p16 revealed variable decreased positivity in all the five excised samples, namely two cutaneous Spitz nevi and three hypopharyngeal MELTUMPs (Figure 3). The sites of the excised lesions and corresponding examination results are shown in Table 1.

After complete staging, no lymph node or distant metastasis was detected, thus, the treatment plan was mainly observation. On the basis of the MELTUMP diagnosis, we arranged an intense follow-up plan for the patient according to the guideline for malignant melanoma, including a thorough skin examination for additional peculiar lesions, palpation of lymph nodes, and fibrolaryngoscopy, with particular attention paid to the hypopharynx every 3 months. The number of the nevus stopped increasing 1 year after the initial eruption, but there was no sign of spontaneous regression. During the subsequent 6 months of follow-up after the removal of the hypopharyngeal MELTUMPs, there was no newly detected melanocytic malignancy.

Discussion

EMN is a rare phenomenon in which hundreds of melanocytic nevi appear suddenly.1 The lesions of EMN can include banal nevi, blue nevi, and Spitz nevi.4 EMN may arise in the setting of blistering skin disease, immunosuppression, cytokine administration, biological agent administration, chemotherapy,1 Addison disease,5 paraneoplastic phenomena,6 pregnancy, and idiopathic causes.1,7 The proposed pathogenesis of EMN includes diminished immune surveillance, genetic susceptibility, and drug adverse effects,1 although the exact pathogenesis is not clearly understood. The chance of potential malignant transformation is assumed to be theoretically higher in patients with EMN. Regular screenings for dysplastic nevi or melanoma have been recommended by many authors.1–6 However, to our knowledge, no melanocytic malignancy has been reported following an EMN eruption in the English-language literature.

The concept of a MELTUMP was first proposed in 2004 as “borderline” melanocytic lesions that are difficult for dermatopathologists to classify as malignant or benign because of their ambiguous morphology.1 In the present case, the pathology of the hypopharyngeal lesions exhibited both benign characteristics (well-circumscribed architecture with maturation and no mitotic activity) and also troubling characteristics (a slightly asymmetrical architecture, confluent cell nests, and frequent pagetoid spread even in the upper half of the epithelium). These lesions could not be classified as merely benign nevi, but they also failed to meet the criteria for melanoma, which is a constellation of multiple atypical findings. Through consultations with dermatopathologists in Taiwan, we concluded that the optimal diagnosis for these lesions is a MELTUMP.

Two recent large case series of MELTUMPs have reported a low risk of nodal metastasis (6–15%) and mortality from distant metastasis during follow-up (1%).5,10 These results suggest that a MELTUMP is a low-grade malignant melanocytic tumor and should be treated according to the guidelines for invasive melanoma.9,10

We performed a careful workup but could not identify any possible underlying diseases or medications related to EMN in this patient. Indeed, most of the cases of EMN have been associated with underlying diseases or medications,5,6 of which the disease courses flare and abate in parallel with the activity of the underlying diseases. However, as in the present case, a few cases of EMN have been reported as being idiopathic, of these cases, the

Table 1 Excision site, pathologic diagnosis, and corresponding examination result.

<table>
<thead>
<tr>
<th>Site</th>
<th>Pathology</th>
<th>BRAF mutation</th>
<th>Percentage of p16 positive cells</th>
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<tbody>
<tr>
<td>Right abdomen</td>
<td>Spitz nevus</td>
<td>Present</td>
<td>&lt; 5% (Figures 3A &amp; 3B)</td>
</tr>
<tr>
<td>Left wrist</td>
<td>Spitz nevus</td>
<td>Absent</td>
<td>Test not performed</td>
</tr>
<tr>
<td>Left abdomen</td>
<td>Spitz nevus</td>
<td>Test not performed</td>
<td>&lt; 5% (Figure 3C)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>MELTUMP</td>
<td>Present</td>
<td>50–60% (Figures 3D &amp; 3E)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>MELTUMP</td>
<td>Test not performed</td>
<td>Test not performed</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>MELTUMP</td>
<td>Present</td>
<td>&lt; 5% (Figure 3F)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>MELTUMP</td>
<td>Test not performed</td>
<td>&lt; 5% (Supplementary Figure 1)</td>
</tr>
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MELTUMP — melanocytic tumor with uncertain malignant potential.
In previous studies, p16 stains for cutaneous or mucosal benign nevi expressed a consistent pattern of diffuse positivity. Unlike previous studies, all the cutaneous Spitz nevi and hyperplaryngeal MELTUMPFs in this case showed considerably decreased percentages of P16 positivity, indicating an underlying aberration of normal senescence pathway.

According to our preliminary results, this is the first study to demonstrate both BRAF and p16 mutation in the same excised EMN tissue, whether these mutations play a combined role in the initiation and subsequent melanogenesis of EMN remains unknown. Because of the limited number of EMN cases, large-scale studies are warranted to establish the consistency of these findings. We hope that these findings can contribute to future studies and treatment options for EMN.

In conclusion, this is the first case of EMN found to have concurrent melanocytic malignancies. We suggest thorough and careful examinations and intense follow-up for patients with EMN, and that fibrolaryngoscopy should always be used as part of the tumor work-up. The BRAF V600E and P16 mutations were speculated in the excised EMN tissues, the significance of which has yet to be determined.

References


Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dsi.2016.05.001.