An interesting case of melanoma with divergent differentiation aberrantly expressing calretinin stain

Chien Sheng Tan¹ and Suyin Ong²

Abstract
Metaplastic melanoma or melanoma with divergent differentiation is a rare variant of melanoma with a wide spectrum of mesodermal and ectodermal differentiation. This is a case of metaplastic melanoma with aberrant expression for calretinin stain in the chondroid component and malignant cells adjacent to it. The finding of calretinin positivity in melanoma could be useful in diagnosing metastatic metaplastic melanoma. The awareness of the possibility of aberrant calretinin positivity in metaplastic melanoma with chondroid differentiation is critical to avoid a potential pitfall in misdiagnosing metaplastic melanoma as sarcoma or mesothelioma.

Keywords
Melanoma, metaplastic melanoma, calretinin

Introduction
Metaplastic melanoma or melanoma with divergent differentiation is a rare variant of melanoma with a wide spectrum of mesodermal and ectodermal differentiation.¹ Metaplastic melanoma commonly has a very thick Breslow thickness and presents at advanced stage. This is a case of metaplastic melanoma with prominent chondroid differentiation. The chondroid component and malignant cells adjacent to it show evidence of calretinin staining on immunohistochemistry study. We present a rare variant of melanoma with aberrant expression for calretinin stain.

Case report
An 83-year-old Asian female was referred with a nodule over the left shin which enlarged over two years. It bled occasionally when accidentally traumatized. Her past medical history was significant for hypertension, osteoporosis and chronic obstructive pulmonary disease, which was stable on amlodipine, alendronic acid, calcium carbonate and vitamin D3 ventolin and tiotropium inhalers. She was able to cope with all activities of daily living. Physical examination revealed a 1.7 cm × 1.4 cm erythematous nodule with an overlying scab, as shown in Figure 1. The base was hyperpigmented. There were no popliteal or inguinal lymphadenopathy. There were no other suspicious lesions on the rest of her skin. The

Figure 1. The lateral aspect of the calf shows a large polypoid pigmented tumour measuring 1.7 cm × 1.4 cm × 1.1 cm. Extensive ulceration is noted on the lesion.

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The tumour was excised with a 5 mm margin down to, but not including, the fascia. The histology of this tumour is shown in Figure 2. The tumour showed surface ulceration and Breslow thickness measuring 11 mm. Chondroid differentiation was noted in the lesion. The chondroid component was seen predominantly in the middle of the lesion and constituted approximately 30% of the lesion. No lymphovascular invasion, evidence of regression, microsatellitosis or perineural invasion was seen. Lymphocytic response was non-brisk. Tumour cells were immunoreactive to melan-A as shown in Figure 3. Melan-A staining was loss in tumour cells with chondroid differentiation. Interestingly, these cells were immunoreactive to calretinin stain, as shown in Figure 4. The tumour was 6 mm from the resection base and 7 mm from the closest skin resection margin.

Immunohistochemistry studies performed on this metaplastic melanoma showed evidence of positive staining for melan-A in the majority of tumour cells except the metaplastic chondroid component. Focal HMB-45 staining was noted within the epithelioid component of melanoma. Interestingly, the area with HMB-45 positivity was also immunoreactive to EMA, CAMS-2 and CKIT. Diffuse cyclin D1, BCL-2, vimentin and P16 staining was noted in the melanoma. Stains for GATA-3, MNF116, SMA, e-cadherin, monoclonal CEA, AE1/3, CD8, CD10, beta catenin, CD30, P63, CD34, AMACR and CD68 were completely negative in tumour cells. P53 staining was focal and unlike the pattern of staining observed on P16 stain. This lesion was reported as a metaplastic melanoma.

Positron emission tomography-computed tomography scan showed mild fluoro-deoxyglucose (FDG) uptake in the left lateral calf, possibly related to post-excision changes, but did not show any evidence of metastatic melanoma. No FDG-avid abdomino-pelvic lymph node was detected. A wider excision was undertaken three weeks later. No residual melanoma was noted in the wider excision specimen. Three benign sentinel lymph nodes were confirmed. However, the patient presented with nodal metastases in the left inguinal lymph nodes after approximately one and a half years from the time of diagnosis.

Discussion

Over the years, numerous review articles on immunohistochemistry studies on melanoma have shown that melanomas are immunoreactive to S100, HMB-45, melan-A, SOX-10, MART-1, Mitf, anti-thyrosinase and vimentin. Aberrant staining for other non-melanocytic markers has been reported in some specific subtypes of melanoma and rare case reports. Metaplastic melanoma represents a rare variant of melanoma with divergent differentiation capable of unusual and aberrant staining for various types of non-melanocytic markers. Aberrant staining for CEA, EMA, keratin markers, calretinin, desmin, SMA, NFP, GFAP, VS38, CD138, CD68 and Factor XIIa has been reported in case reports, review articles and tissue microarray studies on melanoma.

Figure 2. Histology shows a tumour composed of malignant epithelioid and spindled cells with chondroid differentiation. The tumour has a Breslow thickness of 1.1 mm.

Figure 3. Tumour cells are diffusely immunoreactive to melan-A. However, the metaplastic chondroid component is negative for melan-A stain.

Figure 4. This image shows the metaplastic chondroid malignant cells are immunoreactive to calretinin stain. This similar component is also immunoreactive to EMA and P16 stains. Calretinin and EMA stains are negative in the spindle cell component and epithelioid component of melanoma.
Divergent differentiation in this variant of melanoma could pose a diagnostic challenge especially when aberrant expression for various non-melanocytic markers has been reported in metaplastic melanoma.6,57

Calretinin is a calcium binding protein which is structurally related to S100 protein and inhibin. Immunohistochemical stain for calretinin shows nuclear and cytoplasmic staining in mesothelial cells, adipocytes, endometrial stromal cells, ganglion cells, Sertoli cells and Leydig cells. Aberrant staining for calretinin stain is rare in melanoma. To our knowledge, metaplastic melanoma has not been reported to stain for calretinin. Rare incidents of calretinin positive melanoma are reported in epithelioid, pleomorphic and metastatic melanoma.7 However, the pattern of calretinin staining in melanoma is not documented in most case reports and review articles on melanoma.

Conclusions
This case highlights a rare subtype of melanoma which shows calretinin positivity in the area with chondroid metaplastic changes. The finding of calretinin positivity in melanoma could be useful in diagnosing metastatic metaplastic melanoma. The awareness of the possibility of aberrant calretinin positivity in metaplastic melanoma with chondroid differentiation is critical to avoid a potential pitfall in misdiagnosing metaplastic melanoma as sarcoma or mesothelioma.

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