PLEOMORPHIC DERMAL SARCOMA: A UNIQUE PRESENTATION DURING IMMUNOTHERAPY

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Summary

Pleomorphic dermal sarcoma (PDS)is a rare dermal-based tumor, with low-grade malignant behavior. It'sknown for its rapid growth, exophytic nature and tendency to bleed. It commonly occurs in elderly individuals on sun-exposed skin regions and shares similarities with atypical fibroxanthoma (AFX). We present a case of a 55-year-old male patient exhibiting an exophytic lesion on the back of his neck while undergoing immunotherapy because of metastatic Clear cell renal cell carcinoma (ccmRCC).
Key words: *Pleomorphic dermal sarcoma, renal carcinoma, checkpoint inhibitors, nivolumab, ipilimumab.*

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Introduction

Pleomorphic dermal sarcomas (PDS) are rare dermal-based tumors, typically arising in elderly male individuals on sun-exposed skin regions. It shares similarities in clinical and histological appearance and molecular genetics and epigenetics with atypical fibroxanthoma [1]. While both tumors are part of a disease spectrum, distinguishing AFX from PDS is vital, given that PDS is a considerably more clinically aggressive tumor[2].

To differentiate PDS from AFX, specific histological characteristics are considered, such as subcutaneous invasion, tumor necrosis, lymphovascular invasion, and/or perineural infiltration [3]. Currently, dermoscopy, confocal laser scanning microscopy, and optical coherence tomography provide limited diagnostic value for both AFX and PDS.

The International Dermoscopy Society (IDS) has described dermatoscopic features of 40 AFX cases, with the majority exhibiting red and white structureless areas and slightly less than half showing irregular linear vessels [4]. Majority of PDS can be treated with curative excisions. Local recurrence in case series of DPS occurs from up to 28%[1] and distant metastases in 2–20% [3].

In case of suspected metastasis, locoregional lymph node sonography is recommended and treatment is defined in accordance with the results.

Definitive guidelines for evaluation and management of pleomorphic dermal sarcoma remain to be established. There is no data regarding the role of imaging and sentinel lymph node biopsy in patients with this sarcoma without clinical suspicion of a rapidly developing disease [5].

Subsequent irradiation may be necessary if complete resection is not feasible. The efficacy of adjuvant and metastatic disease management is unclear, but recent reports show complete remission with pembrolizumab, an anti-PD-1 immune checkpoint inhibitor [3].

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Case Presentation

"A 55-year-old male patient with ccmRCC presented to the outpatient dermatology clinic because of a rapidly growing bloody nodular growth on the back of his neck. Prior to the appearance of the lesion, four cycles of combined immune checkpoint inhibitors (nivolumab plus ipilimumab) were performed, followed by four cycles of nivolumab. Otherwise, the patient has had his left kidney and spleen removed due to trauma, and is undergoing hemodialysis due to acute right kidney failure. The patient stated that he noticed progression of the lesion after the end of the combined immune checkpoint inhibitors therapy.

Clinical examination revealed a mobile, polypoid ulcerated nodule, approximately 2 cm in diameter, rubbery to the touch. Dermoscopy showed linear blood vessels and structureless white and red areas [Figure 1]. Total body examination showed no similar lesions. Due to high clinical suspicion of malignancy, the lesion was excised.

The excised tissue was sent for histopathological analysis with differential diagnoses of polypoid melanoma, squamous cell carcinoma (SCC), Merkel cell carcinoma, and skin metastases of renal carcinoma.

A histopathological examination [Figure 2] revealed aformation made up of clusters of partly large, epithelioid to spindle-shaped tumor cells, with mitotic rate up to 10 mitoses per mm^2. There were also smaller foci of necrosis, while no lymphocapillary or perineural invasions were found in the examined sections. Immunohistochemically, tumor cells were focally positive

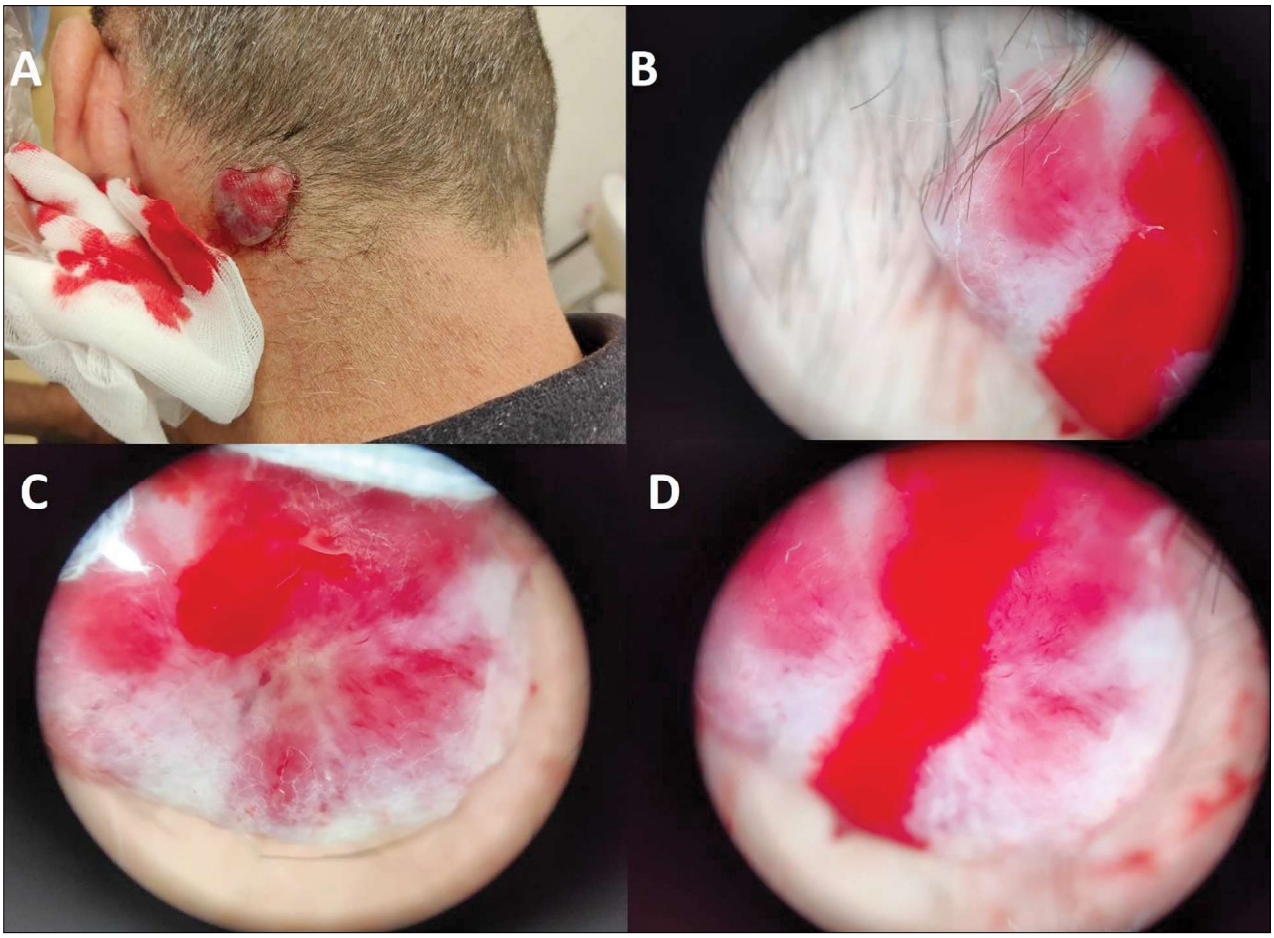

Figure 1 (A) Clinical image of lesion. Dermoscopic images (B, C, D) revealed: linear vessels, red and white structureless areas.

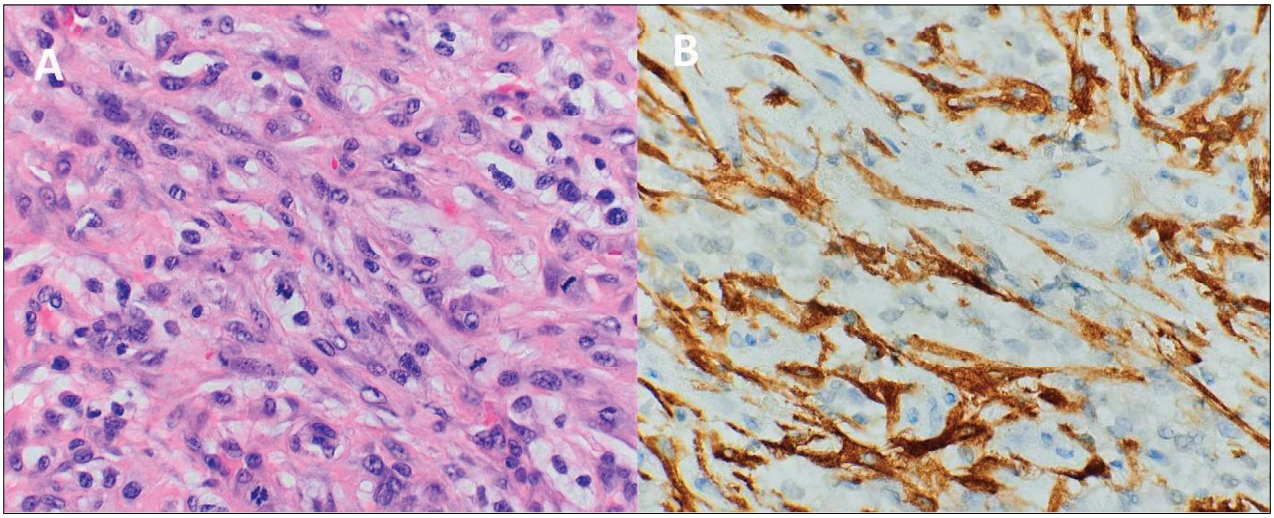

Figure 2. (A) Haematoxylin and eosin (H+E). (B) Immunohistochemical (IHC) staining positive for CD68.

for CD68 and negative for p63, CK5:6, HMB45, Melan A, SOX 10, S100, SMA, DEZMIN. The diagnosis of a PDS was confirmed.

Our hospital's multidisciplinary team for skin tumors was consulted, and due to the patient's good condition, wide excision with a lateral safety margin of at least 2 cm was planned. At the next appointment, a month and a half after tumor excision, the patient presented with a sudden nodule in the area of the right chest [Figure 3], neck and frontal part of the head. Excision of the mentioned changes was performed. Histological findings indicated skin metastases of renal carcinoma.

Considering the worsening of the underlying disease and the new whole-body CT scan results that indicated the progression of meta-static lung disease and the appearance of metastasis in the brain, the planned scar excision was postponed. The patient was referred to an oncologist and due to the progression of the underlying disease, nivolumab was discontinued andaxitinib treatment was started.

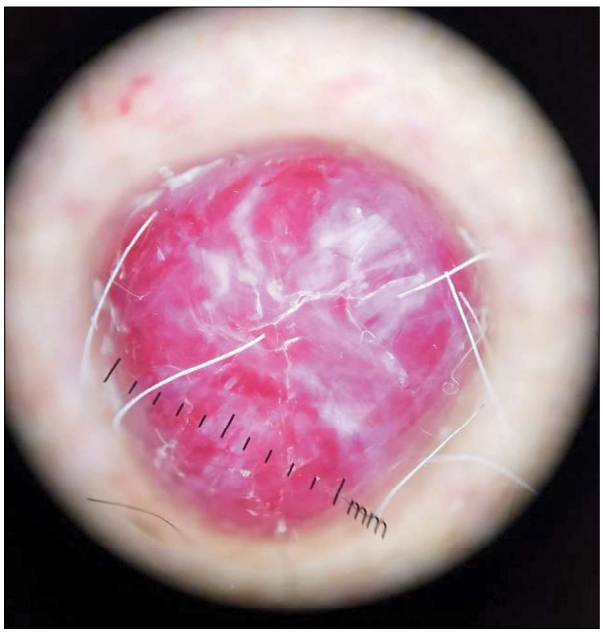

Figure 3. Dermoscopic image revealed: torturous linear vessels, red structureless areas, specific polarizing white structures.

Discussion

The choice of first-line treatment for advanced renal cell carcinoma depends on the risk factors. According to the Croatian Health Insurance Institute guidelines, combination therapy with ipilimumab and nivolumab is approved for the treatment of advanced intermediate or high-risk renal cell carcinoma. The discovery of immune checkpoint inhibitors (ICIs) made a significant impact in the fight against cancer, but at the same time, we encounter specific side effects of treatment with these drugs on an almost daily basis. The side effects of ICIs treatment are autoimmune in nature and can affect any organ system [6,7,8]. The most

commonly affected organs are the skin, thyroid, colon, lung, and liver [6,8].Although ICIs often cause cutaneous immune-related adverse events,PDS has not been reported as a known side effect. PDS are rare dermal-based tumors, typically arising in elderly male individuals on sun-exposed skin regions. According to a meta-analysis by Chu Qiao Lo and associates, the median age of onset of PDS was 80.64 years. Of these, 82.8% of the cases involved men. The disease was mainly present on the skin of the skull, with a significantly smaller percentage on the skin of the face [9].

We think this case is interesting because PDS has progressed during immunotherapy, which is usually used as treatment for advanced PDS with distant metastases. As mentioned, the patient noticed a rapid increase in PDS during treatment with nivolumab alone, after the completion of combined immunotherapy.Moreover, the enlargement of PDS was simultaneous to the clinical progression of metastatic Clear cell renal cell carcinoma.

According to a randomized phase II study (Alliance A091401) in 85 patients diagnosed with metastatic sarcoma who had previously received at least one line of systemic therapy for advanced disease, an overall response rate of 16% was recorded in patients treated with the combination of ipilimumab and nivolumab, while no positive response was recorded in the group of patients treated only with nivolumab[10]F.

Apart from the fact that our patient is significantly younger in comparison to the data found in the literature, we consider this case report to be interesting because PDS followed the progression of the primary tumor, although we believe that it is an independent tumor. The PDS was under control during the combined immunotherapy and progressed after switching to nivolumab alone as primary therapy.

Conclusions

Pleomorphic dermal sarcoma is a rare dermal based tumor. In this case report, we presented the occurrence of pleomorphic dermal sarcoma in a 55-year-old male patient who was undergoing immunotherapy for metastatic Clear cell renal cell carcinoma (ccmRCC). The question of whether the appearance of the tumor is a consequence of immunotherapy or a mere coincidence remains unanswered. However, our view is that it represents an independent, simultaneous occurrence. This perspective is based on the observation that dermal sarcomas have been noted in patients on immunosuppressive therapy but not in those treated with immunotherapy, given the opposite nature of their actions. Further investigations are warranted to explore the potential correlation between immunotherapy and the development of pleomorphic dermal sarcoma.

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Conflict of interest
NONE DECLARED

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