CASE REPORT

Primary mediastinal choriocarcinoma presenting as cutaneous metastasis with resistance to chemotherapy: case report and literature review

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Abstract
Cutaneous metastases of choriocarcinoma are rare. They may indicate poor prognosis and resistance to chemotherapy. In this report, we present a case of a 25-year-old man who presented with central pleuritic chest pain and right upper arm mass for about a week. The patient also had significant weight loss during the last 5 months along with an episode of generalized seizure. Chest computed tomography scan revealed an 8 cm anterior mediastinal mass. A skin punch biopsy from the right upper arm mass revealed a malignant neoplasm with morphology consistent with metastatic choriocarcinoma. Further work-up revealed multiple lung and brain lesions. Ultrasound of the testes revealed no abnormalities. Several chemotherapy regimens were tried; however, there was no response and the disease showed progression. The patient died 6 months after initial presentation.

KEYWORDS
chemotherapy, choriocarcinoma, cutaneous, mediastinum, metastasis

1 INTRODUCTION
Choriocarcinoma is a malignant trophoblastic tumor that occurs most commonly in women of reproductive age following hydatidiform mole, abortion, or normal pregnancy (gestational choriocarcinoma). In men, however, it usually presents as a component of mixed germ cell tumor usually originating in the testis, or in some cases, in extragonadal sites such as mediastinum and retroperitoneum (non-gestational choriocarcinoma).2 Choriocarcinoma tends to metastasize to the lungs, brain, liver, and GI tract.3 However, cutaneous metastases are rare events.2-25 Most of the cases reported in the literature with cutaneous metastasis are testicular choriocarcinomas,2-18 and to a lesser extent, gestational choriocarcinomas.19-25 To the best of our knowledge, no cases of primary mediastinal choriocarcinoma presenting as cutaneous metastasis have been reported in the literature. We describe an unique case of primary mediastinal choriocarcinoma presenting as cutaneous metastasis.

2 CASE PRESENTATION
A 25-year-old man with a history of smoking presented to the emergency department with severe crushing central pleuritic chest pain and right upper arm painless swelling for 1-week duration, along with dry cough, shortness of breath, and sweating. The patient also complained of fatigue with significant weight loss of 5 kg over the past 5 months and reported a single episode of generalized seizure. Physical examination revealed a single, 1.3 cm non-tender, fixed, firm, non-
ulcerating dark erythematous well-demarcated nodule over the medial side of the right upper arm. Computed tomography (CT) scan of the thorax revealed an 8 cm anterior mediastinal mass extending to the pericardium and causing hemorrhagic pericardial effusion along with numerous bilateral lung nodules (Figure 1). Because of impending tamponade, the patient had emergency pericardiocentesis draining around 700 mL of hemorrhagic fluid magnetic resonance imaging (MRI) of the brain revealed a left intra-axial occipito-parietal hemorrhagic mass with rim enhancement suggestive of metastatic disease.

Skin biopsy from the right upper arm mass revealed dermal infiltration by highly pleomorphic mononuclear tumor cells with prominent nucleoli and abundant pale eosinophilic cytoplasm. In addition, there were multinucleated tumor cells with morphologic features of syncytiotrophoblasts. There were areas of geographic necrosis and numerous mitotic figures (Figure 2A-C). Immunohistochemical (IHC) stains showed that the tumor cells were positive for cytokeratin AE1/AE3, SALL4, and beta-HCG (Figure 2D-F), but negative for epithelial membrane antigen (EMA), S100, Melan-A, HMBA45, leukocyte common antigen (LCA), placental alkaline phosphatase (PLAP), OCT3/4, CD117, CD30, alpha-fetoprotein (AFP), cytokeratin 5/6, TTF-1, and napsin A.

CT-guided biopsy from the left lung nodules revealed tumor with similar morphological and IHC features. Left parieto-occipital craniotomy with resection of metastatic brain lesion was performed, which revealed metastatic tumor with similar morphology. No other germ cell tumor components in the skin, lung, and brain were identified. The overall histopathologic findings of the tumor from all sites were interpreted as metastatic choriocarcinoma with primary origin in the mediastinum. Scrotal ultrasonography was performed to rule out the possibility of testicular primary, which revealed no testicular focal lesions.

The patient was started on the first cycle chemotherapy with EP protocol (etoposide and cisplatin), which was complicated by thrombocytopenia and febrile neutropenia. In the second cycle, VIP protocol (etoposide, ifosfamide, and cisplatin) was initiated because of extensive lung metastases and restrictive pattern on pulmonary function test. After three cycles of chemotherapy, serum beta-hCG level was dropped from 68000 to 1300 mIU/mL, indicating a good response. However, MRI of the brain, performed 2 weeks later due to dizziness of new onset, revealed disease progression with new multiple brain lesions. The patient received stereotactic radiosurgery to these new brain metastases. The chemotherapy protocol was changed to TIP protocol (paclitaxel, ifosfamide, and cisplatin) as a salvage therapy. He received only two cycles. However, follow-up positron emission tomography–computed tomography scan revealed increased uptake of mediastinal primary, and rise in serum beta-hCG levels. Discussion regarding autologous stem cell transplant was carried on, but as the disease did not achieve complete remission, the procedure was postponed.

The patient was then started on EMA/CO protocol (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine). MRI of the brain performed 1 week later revealed progression of the disease with multiple small newly developed lesions. Chemotherapy was continued with intrathecal methotrexate and whole brain palliative radiotherapy was administered. A paraffin block was sent to a reference laboratory for further testing to identify any actionable biomarker for possible targeted therapy. IHC testing for mismatch repair (MMR) proteins performed on formalin-fixed and paraffin-embedded tissue (FFPE) did not show loss of nuclear expression of MMR proteins; low probability of microsatellite instability-high (MSI-H). The biomarker programmed death-ligand 1 (PD-L1) was found to be positive (2+ intensity in 10% of tumor cells). Pathogenic mutation at the exon 2 of PTEN gene was detected by next-generation sequencing.

Despite these results, a week later, the patient’s condition markedly deteriorated as he developed fever along with hemoptysis and sputum production. He was diagnosed to have hospital-acquired pneumonia with respiratory failure. The patient did not respond to further therapy and died.

3 | DISCUSSION

Choriocarcinoma is a malignant trophoblastic tumor that is characterized by proliferation of cytotrophoblasts, intermediate trophoblasts, and syncytiotrophoblasts in the absence of chorionic villi. In women of reproductive age, it mostly presents as an aggressive form of gestational trophoblastic disease most commonly following hydatidiform mole (gestational choriocarcinoma). In men, however, it is found usually as a component of mixed germ cell tumors (non-gestational choriocarcinoma).1

Primary choriocarcinomas of the mediastinum are rare as in most cases the tumor is metastatic from a gonadal primary. Arendt et al reported the first case of primary mediastinal choriocarcinoma in 1931,26 and since then, fewer than 50 cases have been reported.27-31 Primary mediastinal choriocarcinoma with metastasis to the lungs,28 brain,29 stomach30 and choroid31 have been described; however, to the best of our knowledge, no cases of primary mediastinal choriocarcinoma presenting as cutaneous metastasis have been reported so far.

In our case, histopathologic examination of the biopsies taken from the sites of metastasis (skin, lung, and brain) showed similar and consistent morphological and IHC features. Morphologically, the

**FIGURE 1** Chest computed tomography-scan reveals an anterior mediastinal mass (blue arrows) and multiple metastatic lung nodules (red arrows)
tumor had a biphasic pattern comprising highly pleomorphic mononuclear cells intermixed with scattered atypical hyperchromatic multinucleated cells, with extensive necrosis and numerous mitotic figures. The overall picture was that of a poorly differentiated neoplasm. IHC stains were performed to further characterize the tumor. The tumor cells were negative for melanoma makers (S100, Melan-A, and HMB-45). Lymphoma was also excluded as LCA was negative. The tumor was positive for cytokeratin AE1/AE3, consistent with epithelial origin. Pulmonary primary was considered; however, the tumor cells were negative for lung adenocarcinoma markers (TTF-1 and napsin A). The tumor cells showed focal nuclear positivity for p40 and p63; however, high molecular weight cytokeratin (cytokeratin 5/6) was completely negative and poorly differentiated squamous cell carcinoma was excluded. The presence of multiple bilateral variable-sized lung nodules by imaging were suggestive of lung metastasis rather than lung primary as well. Finally, the tumor cells showed strong nuclear staining for SALL4, a sensitive marker for tissue origin. Markers for embryonal carcinoma (CD30), seminoma (OCT3/4 and CD117), and yolk sac tumor (AFP) were negative. The overall morphological and IHC features were consistent with choriocarcinoma. After the exclusion of testicular focal lesions by scrotal ultrasonography and the demonstration of dominant mediastinal mass by chest CT scan, the tumor was eventually considered of mediastinal origin.

Cutaneous metastasis of choriocarcinoma is very rare. Most of the cases reported in the literature are non-gestational choriocarcinomas arising from testis with a few reported cases of cutaneous metastasis following gestational choriocarcinoma (Table 1) with a few reported cases of cutaneous metastasis following gestational choriocarcinoma (Table 2). Some reported cases in the literature suggest that the presence of cutaneous metastasis in choriocarcinoma may indicate poor prognosis. Chhieng et al reported a case of choriocarcinoma presenting as cutaneous metastasis where the patient died 10 days after the initiation of chemotherapy. Shimizu et al reported a case of metastatic choriocarcinoma to the skin; the patient in that case died 3 months after the appearance of cutaneous metastasis. Weijin et al recently reported a case of testicular choriocarcinoma with cutaneous and systemic metastasis, where the patient died after 2 months despite treatment with surgery and chemotherapy. The tumor in our case was resistant to different regimens of chemotherapy and had an aggressive clinical course.

As the tumor in our case was resistant to various chemotherapeutic regimens, it was decided by the tumor board to do further testing for possible targeted therapy. Further IHC testing performed in a reference laboratory revealed that PD-L1 was positive in the tumor. Various clinical trials showed that expression of PD-L1 by tumor cells and immune infiltrates reflects an immune-active microenvironment and would indicate a good response for immunomodulatory agents. In addition, next-generation sequencing that was performed on the DNA extracted from the tumor by microdissection technique, detected a pathogenic mutation at exon 2 of PTEN gene with p.A39 protein.

**FIGURE 2** A, photomicrograph depicting skin in which the dermis is infiltrated by poorly differentiated neoplasm with areas of geographic necrosis (Hematoxylin & Eosin stain, ×40). B, the tumor has biphasic pattern composed of mononuclear cytotrophoblasts and multinuclear syncytiotrophoblasts with extensive necrosis (Hematoxylin & Eosin stain, ×100). C, high power view shows atypical mononuclear cytotrophoblasts (arrowheads) and multinuclear syncytiotrophoblasts (arrows) (Hematoxylin & Eosin stain, ×200). D, the tumor cells demonstrate strong and diffuse staining for cytokeratin AE1/AE3 (IHC, ×100). E, strong nuclear reactivity for SALL4 (IHC, ×100). F, strong diffuse reactivity for beta-hCG (IHC, ×100).
alteration. PTEN gene has been found to be mutated in various human cancers. Tumors with PTEN gene mutation were found to respond to poly (ADP-ribose) polymerase (PARP) inhibitors. The patient’s condition, however, deteriorated rapidly precluding any kind of immune or targeted therapy.

In summary, we are reporting the first case of primary mediastinal choriocarcinoma presenting as cutaneous metastasis that was resistant to different chemotherapy regimens. The results of our case support the findings of previously reported cases in the literature that cutaneous metastasis in choriocarcinoma may suggest an ominous prognosis; however, further evidence is needed. The findings in our case may contribute in improving and modifying therapeutic modalities for metastatic choriocarcinoma in the future.

ACKNOWLEDGMENT
The publication of this article was funded by the Qatar National Library.

CONFLICT OF INTEREST
The authors declared no potential conflicts of interest.

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TABLE 1  Cases of testicular choriocarcinoma with cutaneous metastasis

| Case | Author (ref) | Year | Age | Site of skin metastasis |
|------|--------------|------|-----|------------------------|
| 1    | Marka et al² | 2019 | 25  | Scalp                  |
| 2    | Marka et al³ | 2019 | 32  | Cheek and chin         |
| 3    | Weijin et al⁴ | 2018 | 18  | Back                   |
| 4    | Toberer et al⁵ | 2018 | 19  | Scalp                  |
| 5    | Elkeeb et al⁶ | 2018 | 18  | Lip                    |
| 6    | Geramizadeh et al⁷ | 2012 | 26  | Chin                   |
| 7    | Bonilla et al⁸ | 2011 | 38  | Chest                  |
| 8    | Muller et al⁹ | 2010 | 16  | Shoulder               |
| 9    | Chen et al⁹  | 2010 | 34  | Neck                   |
| 10   | Chen et al⁹  | 2010 | 29  | Arm                    |
| 11   | Hapa et al¹⁰ | 2008 | 23  | Scalp and chest        |
| 12   | Senapati et al¹¹ | 2008 | 23  | Back                   |
| 13   | Bhatia et al¹² | 2007 | 22  | Chin and chest         |
| 14   | Sofikerim et al¹³ | 2005 | 42  | Chin                   |
| 15   | Tinkle et al¹⁴ | 2001 | 24  | Chin, jaw and scalp    |
| 16   | Shimizu et al¹⁵ | 1996 | 22  | Back                   |
| 17   | Chhieng et al¹⁶ | 1995 | 23  | Back                   |
| 18   | Requena et al¹⁷ | 1991 | 23  | Chest                  |
| 19   | Winter et al¹⁸ | 1989 | 27  | Shoulder               |

TABLE 2  Cases of gestational choriocarcinoma with cutaneous metastasis

| Case | Author (ref) | Year | Age | Site of skin metastasis |
|------|--------------|------|-----|------------------------|
| 1    | Choi et al¹⁹ | 2015 | 30  | Scalp                  |
| 2    | Razi et al²⁰ | 2011 | 47  | Back                   |
| 3    | Mendez et al²¹ | 2009 | 23  | Finger                 |
| 4    | Afshar et al²² | 2007 | 33  | Finger                 |
| 5    | Park et al²³  | 2005 | 52  | Back                   |
| 6    | Chama et al²⁴ | 2002 | 40  | Chest                  |
| 7    | Cosnow et al²⁵ | 1974 | 29  | Scalp                  |
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How to cite this article: Murshed KA, Kanbour A, Akhtar M, Al Hyassat S. Primary mediastinal choriocarcinoma presenting as cutaneous metastasis with resistance to chemotherapy: case report and literature review. J Cutan Pathol. 2021;48(1):81–85. https://doi.org/10.1111/cup.13777