

CASE REPORT

p40 in metastatic pulmonary trophoblastic tumour: potential diagnostic pitfall on histopathology

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Abstract

p40, one of the two isomers of p63, is nowadays widely used for diagnosis of squamous cell carcinoma, especially in subtyping non-small cell carcinoma on lung biopsies. We describe a case in which lung tumour was misdiagnosed as squamous cell carcinoma due to p40 immunopositivity. A 36-year-old lady presented with cough and left sided chest pain of 2 months duration. Chest imaging revealed a lesion in left lower lobe of the lung and biopsy was suggestive of squamous cell carcinoma. However, past history revealed amputation of great toe for non-healing discharging ulcer which on histopathology was diagnosed as choriocarcinoma. She also had a history of hysterectomy five years ago, details of which were not available. Post-amputation β -hCG levels were high and she had been treated with multimodality chemotherapy for choriocarcinoma. She had good response to chemotherapy initially, however became resistant later on. Review of the lung biopsy in the light of the past history along with extensive literature review led to the final diagnosis of metastatic trophoblastic tumour to lung. Hence, awareness that p40 immunopositivity can be seen in trophoblastic tumours is essential to avoid misdiagnosis, especially in sites like the lung where squamous cell carcinoma is common.

Keywords: p40, immunohistochemistry, trophoblastic tumours, lung metastases

INTRODUCTION

p40, one of the two isomers of p63, is a sensitive and specific marker for squamous cell carcinoma (SCC). Recent studies have found that p40 is in fact superior to p63 in diagnosing SCCs of various anatomical sites.^{1,2} In addition to SCC, p40 immunorexpression has been noticed in thymomas, urothelial carcinomas, trophoblastic tumours, myoepithelial cells of breast, skin adnexal tumours and basal cells of the prostate.^{1,3-5}

Though p40 is nowadays widely used for the diagnosis of SCC, especially for subtyping non-small cell lung carcinomas, the awareness that this antibody may be expressed in trophoblastic tumours is limited. We describe a case in which lung biopsy was misdiagnosed as SCC due to p40 immunopositivity. Relevant past history along with extensive literature review led to the final diagnosis.

CASE REPORT

A 36-year-old woman presented in January 2014 with cough and left sided chest pain of 2 months duration. Computed tomography (CT) revealed a lesion in left lower lobe of the lung, from which a CT-guided biopsy was taken. Further clinical details were not available at this stage.

The biopsy revealed an invasive tumour composed of polygonal cells with moderate amount of eosinophilic cytoplasm, round to oval nuclei and inconspicuous nucleoli. Occasional mitotic activity and focal necrosis were noted. No keratin was seen though some hyaline eosinophilic material was observed. As there was no differentiation towards any specific lineage, TTF-1 and p40 immunostains were performed. These tumour cells were immunopositive for p40 and immunonegative for TTF-1. A diagnosis of non-small cell lung carcinoma, favouring squamous cell carcinoma was offered on this biopsy (Fig. 1).

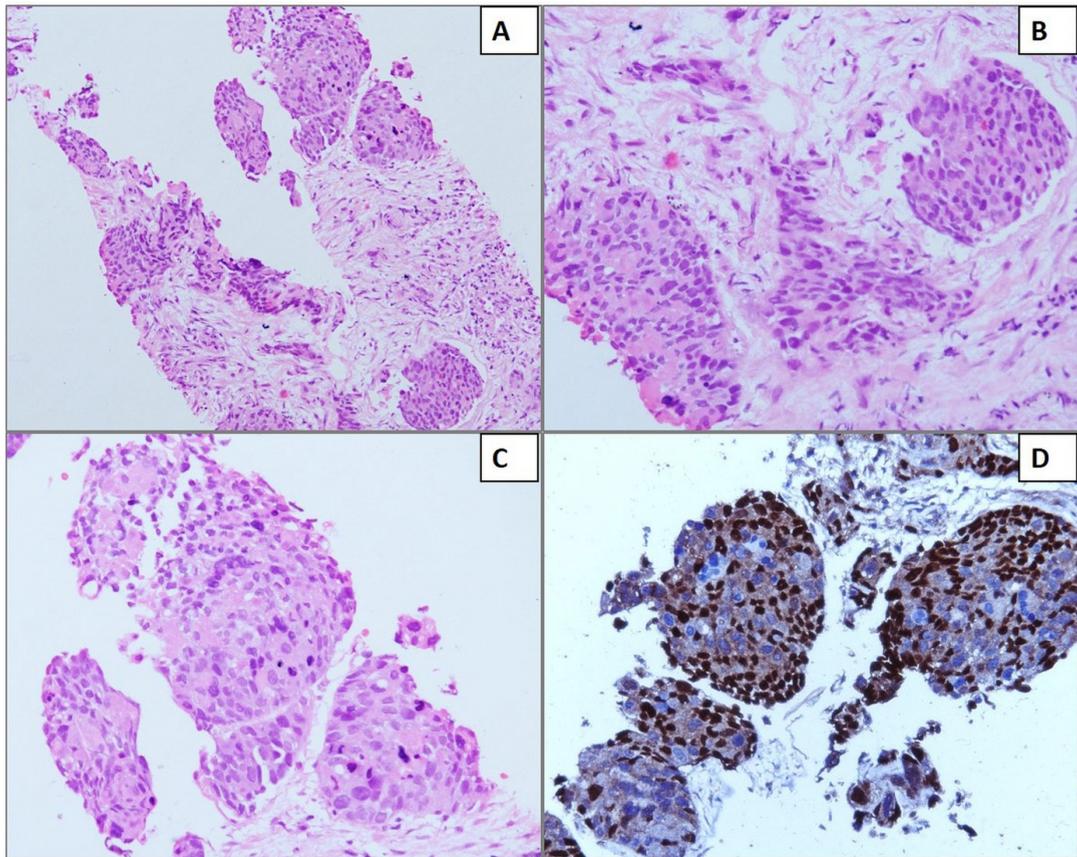


FIG. 1: (A) The lung biopsy shows an invasive tumour (H&E, 10x); (B) composed of polygonal cells with moderate amount of eosinophilic cytoplasm, round to oval nuclei and inconspicuous nucleoli (H&E, 20x). (C) Hyaline eosinophilic material is seen amid tumour cells with mitotic activity (H&E, 20x). (D) These tumour cells show strong nuclear immunopositivity for p40 in approximately half of the tumour cells (IHC, 20x)

Past history

Following this, we received detailed past history with a request to review the case. She presented to the surgery outpatient department in 2011 with a non-healing discharging ulcer on the great toe for last 6 months. A clinical diagnosis of chronic osteomyelitis was made and she underwent amputation of the toe. A month later she developed similar nodules and ulcers over the left arm, followed by a gradually worsening dry cough and progressive shortness of breath. She was a non-smoker. On imaging, she was found to have a septated left sided pleural effusion. The fluid was exudative, however there were no acid fast bacilli on microscopy and it was sterile on culture. An intercostal drain was inserted and empirical anti-tubercular drugs were added, without any significant relief over the next 3 weeks. A positron emission tomography-computed tomography (PET-CT) revealed a large

hypermetabolic soft tissue mass in left lower lobe with bilateral lung metastases and multiple liver deposits. Meanwhile the histopathology report of the amputated great toe was traced and it showed a lobulated malignant tumour. The tumour cells were arranged in sheets, had abundant clear cytoplasm and moderately pleomorphic nuclei including multinucleated cells. Frequent mitotic activity, large areas of haemorrhage, necrosis and cystic change was noted. The tumour infiltrated into the underlying bone. Immunostain for human chorionic gonadotropin (hCG) showed strong positivity, suggestive of choriocarcinoma (Fig. 2).

On reviewing her obstetric history, she had three full term deliveries. She had undergone hysterectomy in 2009 for menorrhagia at a rural clinic and no histopathology records were available.

Serum beta-human chorionic gonadotropin (β -hCG) at this stage was 77800 mIU/ml. A

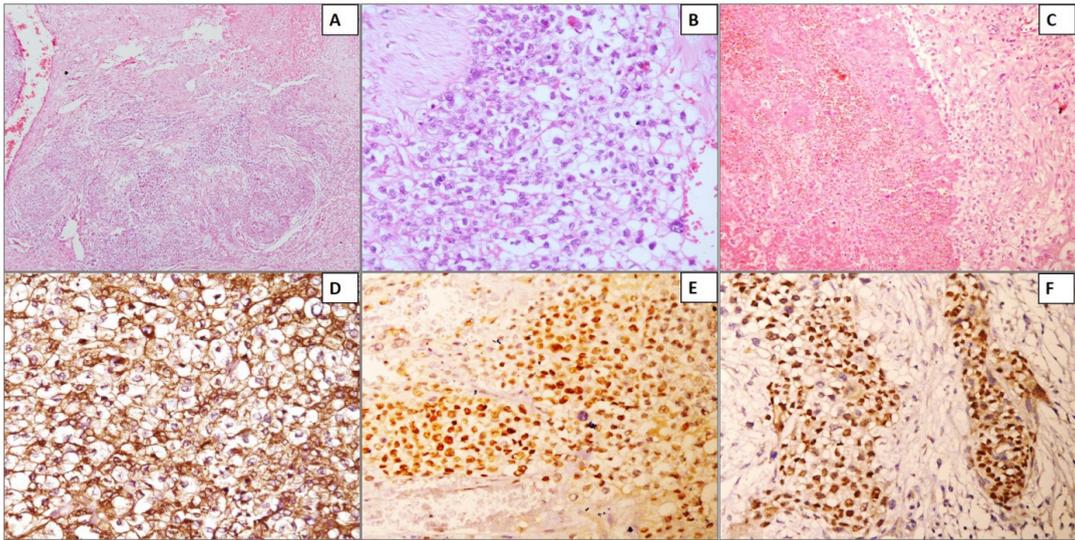


FIG. 2: Great toe amputation specimen shows (A) islands of tumour with infiltrative margins (H&E, 4x). (B) The tumour cells have abundant clear cytoplasm with moderately pleomorphic nuclei (H&E, 20x). (C) Large areas of haemorrhage and necrosis is noted (H&E, 10x). Immunostains for (D) hCG, (E) p63 and (F) p40 show diffuse and strong positivity (D-F, IHC, 20x)

diagnosis of high risk choriocarcinoma was made and she was started on EMA-CO (Etoposide, Methotrexate, Actinomycin D, Vincristine, and Cyclophosphamide) regimen. In November 2012 she completed 8 cycles and achieved a complete remission with normal β -hCG levels of 4.76 mIU/ml.

However, in January 2013, she relapsed with a rising β -hCG level (567.4 mIU/ml) and was started on BEP (Bleomycin, Etoposide, Cisplatin) regimen (4 cycles till April 2013), but β -hCG rose again after a transient fall. In view

of poor response, EMA-EP (EMA alternating with Etoposide, Paclitaxel) was initiated (3 cycles from May–July 2013), followed by EP till October 2013, to achieve a partial response with presence of PET active residual lesion in lung and β -hCG levels of 6.7 mIU/ml. A few months later in December 2013, β -hCG level rose again to 3592 mIU/ml and she developed new lesions in the lung along with nodules over arm. These lung lesions and arm nodule were then biopsied.

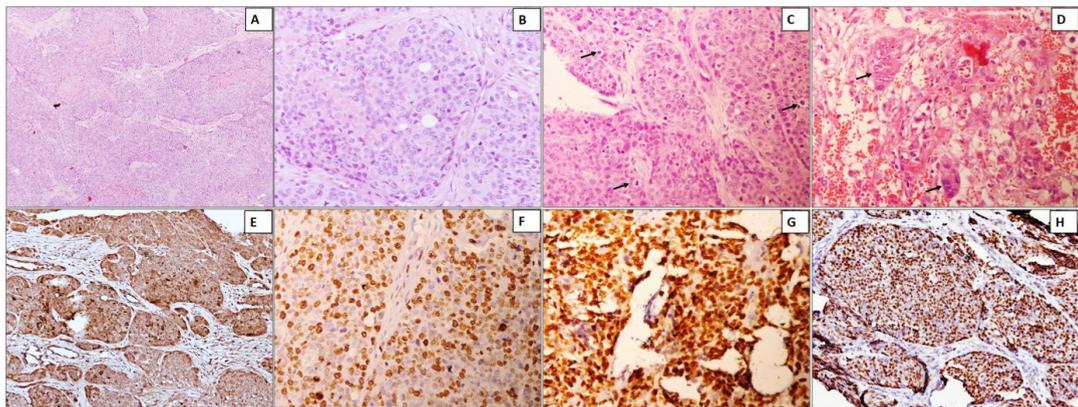


FIG. 3: Excision biopsy of skin nodule over arm shows (A) lobules of tumour cells with areas of necrosis (H&E, 4x). (B) The tumour cells have pleomorphic nuclei and similar hyaline eosinophilic material as seen in lung biopsy (H&E, 20x). (C) Frequent mitosis and presence of (D) syncytiotrophoblasts are noted (H&E, 20x). (E) Immunostains for hCG shows diffuse positivity (10x) with (F) MIB-1 labelling index around 80% (20x). (G) p63 (20x) and (H) p40 (10x) show diffuse nuclear immunopositivity (E-H, IHC)

Biopsy review

In the light of past history, the present lung biopsy was reviewed and further immunostaining for β -hCG was done. Past history of choriocarcinoma, along with literature supporting p40 positivity in trophoblastic tumour and β -hCG immunopositivity in the current biopsy led to the final diagnosis of metastatic trophoblastic tumour over a primary SCC in the lung. Excision biopsy of the skin nodule over the arm done subsequently, also showed similar features (Fig. 3).

Clinical course

Six months later, in June 2014 she presented with partial seizures and left sided hemiparesis. Contrast-enhanced CT of the brain showed a space occupying lesion in the right frontal lobe. She received palliative radiotherapy (5 cycles of 20 Gy) followed by alternating cycles of TP / TE (Paclitaxel, Cisplatin / Paclitaxel, Etoposide) regimen. She had progressive disease with severe left sided chest pain due to recurrent lesions and the β -hCG level rose to >200000 mIU/ml even after 2 cycles. Though the regimen was again changed to VeIP (Vinblastin, Iphosphamide, Cisplatin), β -hCG levels worsened after 2 cycles. In view of brain involvement, high dose Methotrexate (HDMTX) + Etoposide regimen was tried. However β -hCG kept rising. Thereafter, at the tumour board meeting it was decided not to offer further chemotherapy and to continue with palliative care. From December 2014, she was started on a metronomic regimen of oral Capecitabine 500 mg twice a day. She did not come for review thereafter and was lost to follow-up.

DISCUSSION

The present patient likely had gestational choriocarcinoma, as she had a history of per-vaginal bleeding for which hysterectomy was done and had elevated beta-hCG levels. Moreover the reproductive age group is the most common age group affected by gestational choriocarcinoma following term pregnancies. However, confirmatory evidence in the form of histopathology of the hysterectomy specimen was not available.

Choriocarcinoma consists of a trimorphic population of cells including cytotrophoblasts, syncytiotrophoblast and intermediate trophoblast.⁶ On histology, an invasive tumour with marked nuclear atypia and high mitotic rate along with large areas of haemorrhage and

necrosis is seen. Though these features were not overtly evident in the small lung biopsy, great toe and skin nodule excision biopsies display characteristic features of trophoblastic tumour. Primary lung SCC with ectopic β -hCG production and epithelioid trophoblastic tumour (due to the presence of epithelioid morphology) were considered as differential diagnoses. SCC with β -hCG secretion has been reported in head and neck, oesophageal, lung, cervical and vulval SCCs.⁷⁻¹³ However, these case reports showed minimal to moderate elevation of β -hCG (2000-12000 mIU/ml) whereas our case showed marked elevation (77000-200000 mIU/ml). In addition to β -hCG levels, absence of squamous lineage differentiation in the form of keratin pearls and intercellular bridges excluded the possibility of primary pulmonary SCC. Epithelioid trophoblastic tumours (ETT) usually have β -hCG <2000 mIU/ml and are composed of a monomorphic population of tumour cells exhibiting mild to moderate atypia along with a pushing margin. On immunohistochemistry, these tumours have diffuse p63 positivity with hCG positivity in scattered cells and MIB labelling index >10%.^{6,14,15} However, the great toe amputation specimen and excision biopsy of skin nodule showed polymorphic population of cells including syncytiotrophoblasts, marked cellular atypia and diffuse hCG immunopositivity. Nevertheless a possibility of combined epithelioid trophoblastic tumour with choriocarcinoma cannot be completely excluded as described before.¹⁶ The points which favour a component of ETT in this case are non-responsiveness to chemotherapeutic agents, predominance of mononuclear tumour cells with eosinophilic hyaline like degeneration in lung and arm nodule biopsies along with diffuse p63 and p40 positivity on IHC. The great toe showed typical choriocarcinoma areas while arm nodule biopsy showed transition areas between ETT and choriocarcinoma. Diffuse immunopositivity of hCG, elevated Ki-67 labelling index and high serum β -hCG support coexistent choriocarcinoma.

Literature on p40 positivity in trophoblastic cells and trophoblastic tumours are sparse. A recent study on various normal tissues and tumours observed that one-third of normal placenta show p40 immunopositivity.¹⁷ Immunohistochemical studies by Shih *et al* have noted that both isomers of p63 (Δ N isomer, detected by p40 antibody and TA isomer) stained cytotrophoblasts and chorionic-type intermediate trophoblasts, while

they were negative in syncytiotrophoblast and implantation-site intermediate trophoblast. However, p40 immunopositivity was limited to cytotrophoblasts. Approximately a third of choriocarcinomas included in their study revealed p40 immunopositivity which stained <5% tumour cells.¹⁴ Similar findings were seen in the study by Zhang *et al*, where p63 and p40 expression in choriocarcinoma was seen at much lower frequency than that in normal placenta or hydatidiform mole.¹⁸ Extensive literature search revealed only these three studies relating p40 and its expression in trophoblasts or trophoblastic tumours. The present case is interesting as it showed p40 immunopositivity in a majority of tumour cells along with p63 positivity.

To conclude, awareness that p40 immunopositivity can be seen in trophoblastic tumours is essential to avoid misdiagnosis, especially in sites like the lung where SCC is common. Inclusion of relevant past history in the histopathology requisition form is indispensable to make an accurate diagnosis. Further studies are warranted to analyse p40 expression pattern in combined trophoblastic tumours and to see if there is any correlation between diffuse p40 positivity and aggressive behaviour of the tumour, as was seen in the present case.

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