

Secondary malignant melanoma in primary mediastinal germ cell tumour

Abdul Hannan,¹ Noreen Akhter,² Ather Saeed Kazmi,³ Narjis Muzaffar⁴

Abstract

Secondary transformation in Germ Cell Tumours (GCT) is an extremely rare event. We report here a case of malignant melanoma arising in primary mediastinal GCT. A young male presented with new onset dyspnoea and a mediastinal mass. As serum alpha fetoprotein was raised, a diagnosis of primary mediastinal GCT was made. He achieved remission with standard chemotherapy and resection of the mass. After a year, he relapsed with widespread disease which on work-up revealed malignant melanoma. As examination for cutaneous melanoma was unremarkable, a diagnosis of mediastinal GCT with secondary transformation to melanoma was made. Exact origin of melanoma in GCTs is unknown, but these may occur from transformation of dermal elements or de-differentiation of germ cells to melanomas. Before making such a diagnosis, search for primary cutaneous melanoma is mandatory. No clear guidelines exist in literature for the treatment of secondary melanomas, so current management guidelines for cutaneous melanoma may be followed.

Keywords: Teratoma, Malignant, Melanoma, Extra-gonadal Germ Cell tumour, Mediastinal.

Introduction

Germ cell tumours (GCTs) are common neoplasms of young age. Although the most common site in males is testis, but 10% of GCTs are extra-gonadal, mediastinum being the most common primary site.¹ Like other germ cell malignancies, mediastinal GCTs may be seminomas, or non-seminomas or mixed germ cell tumours. Teratoma includes elements originating from all the three germ cell layers (ectoderm, mesoderm and endoderm) like skin, hair, smooth muscle, respiratory and intestinal epithelium; each of which has a potential to undergo secondary transformation.²

Extra-gonadal GCTs are thought to develop from germ cells that have abnormally migrated to central midline

¹Department of Medical Oncology, ²Department of Pathology, ^{3,4}Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan.

Correspondence: Abdul Hannan. Email: abdulhannan103@hotmail.com

structures during embryogenesis. Teratomatous components in mediastinal GCTs have a special tendency for secondary transformation to squamous cell carcinomas (SCCs), adenocarcinomas and sarcomas or melanomas.³ Though rare haematologic malignancies have been reported.⁴ Secondary transformations may occur simultaneously with primary GCTs after chemotherapy completion or remotely. These secondary malignancies usually behave differently from primary tumour and take the characters of secondary malignant change.

Management of mediastinal GCTs includes multi-agent chemotherapy with addition of surgery for non-seminomas. Overall, mediastinal non-seminomas have a worse prognosis than their testicular counterparts.⁵ Treatment of secondary malignancies depends on its nature, type and whether it is metastatic or non-metastatic on standard oncological principles.

Case Report

A 31-year-old male presented in August 2012 with dyspnoea of two weeks' duration. An X-ray and computed tomography (CT) chest showed a huge mass occupying

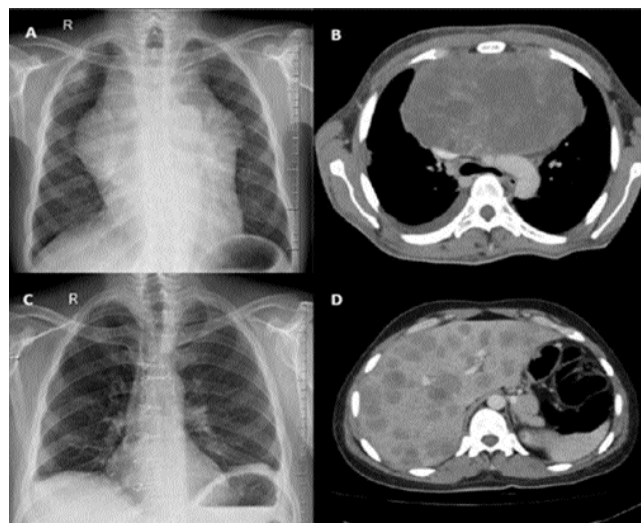


Figure-1: (A) Chest X-ray at baseline showing a huge mediastinal mass. (B) Baseline computed tomography (CT) scan of chest showing mediastinal mass and small right pleural effusion. (C) Chest X-ray after initial treatment and surgery showing normal mediastinal diameter and surgical clips in place. (D) CT scan at relapse: multiple hypodense metastatic lesions in hepatic parenchyma.

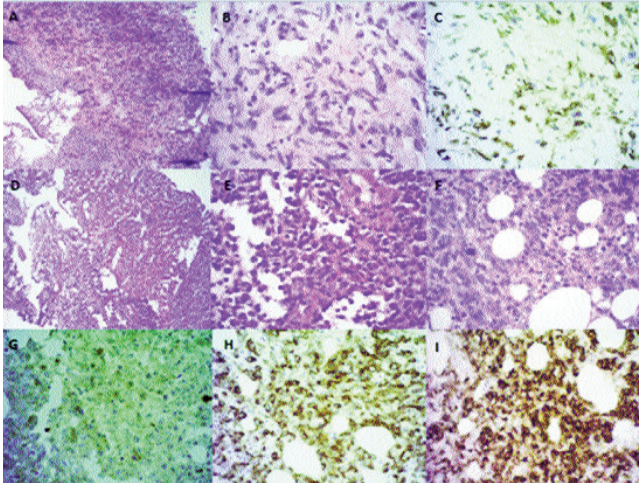


Figure-2: (A and B) Haematoxylin and eosin (H&E) staining on mediastinal mass biopsy at light microscopy and 40x showing neoplastic round to oval and spindle shaped cells with hyperchromatic nuclei. (C) SMA staining which was focally positive in tumour cells. (D and E) Round to polygonal cells with moderate eosinophilic cytoplasm, round vesicular to hyperchromatic nuclei and prominent nucleoli on liver biopsy at light microscopy and at 40x. (F) Bone marrow biopsy at 40x showing replacement of normal marrow with tumour cells. (G) S100 staining of tumour cells. (H) Melan A immunostain which was strongly positive. (I) HMB-45 antibody staining which is also intensely positive in tumour cells.

anterior mediastinum (Figure 1A and B). Scrotal ultrasound did not reveal any testicular mass. At baseline, serum alpha fetoprotein (AFP) was high (1283 IU/ml), lactate dehydrogenase (LDH) was slightly raised (573 IU/ml), but beta human chorionic gonadotropin (B-hCG) was normal. Histopathology of mediastinal mass showed respiratory epithelium with neoplastic round to oval and spindle shaped cells with hyperchromatic nuclei (Figure-2A and B). The only immunostain positive was smooth muscle actin (SMA) favouring smooth muscle differentiation (Figure-2C). Although placental alkaline phosphatase (PLAP), CD-117 and AFP immunohistochemical stains were negative, the diagnosis of Primary Mediastinal Germ Cell Tumour (PMGCT) was made as this was the highest possibility at this young age with raised AFP. The patient was started on bleomycin, etoposide and cisplatin chemotherapy. After 2 cycles of chemotherapy, serum AFP came down to 9 IU/ml and lactate dehydrogenase (LDH) was 560 IU/ml. However, as patient was complaining of increasing dyspnoea, a CT chest showed the mediastinal mass to be growing. The impression made at this time was either a growing teratoma syndrome or a sarcoma element that was non-responsive to chemotherapy. He was, therefore, switched to etoposide, ifosfamide and cisplatin chemotherapy for the next two cycles. After planned chemotherapy, tumour markers normalised and residual mediastinal mass was

resected. Histopathology of this mass revealed no viable tumour, but mature teratoma elements were seen. The patient remained on follow-up with markers and interval imaging (Figure-1C) without any evidence of recurrence till November 13, when he again presented with backache, right hypochondrial pain and raised LDH (1286 IU/ml). AFP and B-hCG were normal. A restaging CT revealed pulmonary and hepatic metastasis (Figure-1D). As the tumour markers were normal, impression of metastatic sarcomatous element or teratoma with secondary transformation was made. The patient was subjected to a bone marrow and liver biopsy. On microscopy, the tumour was composed of round to polygonal cells with moderate eosinophilic cytoplasm, round vesicular hyperchromatic nuclei and prominent nucleoli (Figure-2D and E). Marrow showed 90% cellularity, of which 40% was replaced by the metastatic disease with extensive necrosis (Figure-2F). Immunostains for lymphoma, including LCA, CD-20, CD-30 and CD-138, were unremarkable excluding haematological primary. CD-31 negativity ruled out angiosarcoma, while cytokeratin, desmin, SMA, OCT-4, CD-117 were all negative and excluded metastatic carcinoma as well as GCT. All this inconclusive immunohistochemistry created a diagnostic dilemma and further stains were applied, including S-100 which was only focally positive (Figure 2G). At this time rare possibilities were considered and Vimentin, Melan-A and HMB-45 were obtained (Figure 2H and I). All three were strongly positive, suggesting a diagnosis of malignant melanoma. Upon histopathological confirmation of malignant melanoma, a search was made for any possibility of primary cutaneous melanoma which was inconclusive. Final diagnosis depending on this histopathology was made as malignant melanoma arising as a secondary malignancy in teratomatous component of PMGCT. Mutational analysis revealed wild type BRAF status. As literature was scarce in this particular scenario, the patient was referred for standard treatment of BRAF mutation negative, stage IV melanoma with monoclonal antibody Ipilimumab. However, he died before the treatment could be initiated due to extensive metastatic disease.

Discussion

Mediastinal GCTs constitute approximately 10-15% of all the primary mediastinal tumours. Approximately 33% of the GCTs associated with secondary malignancy occur in mediastinum.⁶ Malignant transformation in GCTs is rare and melanoma as a secondary tumour is even rarely reported. To the best of our knowledge, this is the second case report of malignant melanoma in PMGCT.

A PubMed search including key terms of "germ cell

tumour" and "melanoma" revealed only one case reported in 2012.⁶ It reported melanoma as a secondary transformation in a 32-year-old male patient with PMGCT who was treated with primary chemotherapy and surgical resection of mass. The case relapsed with hepatic metastasis after 13 months of treatment. In particular, that study suggested the origin of malignant melanoma from the respiratory epithelium in mixed GCT. Similar to this case, the germ cell components in our case responded very well to chemotherapy and surgery, but as none of the agents in Bleomycin, Etoposide, Platinol (BEP) are active against melanoma it, therefore, metastasised to other places after secondary transformation in PMGCT. Clinically, our case also relapsed after approximately a year of primary treatment. As compared to the earlier case, in our case report respiratory epithelium was also found on upfront mediastinal biopsy, but melanomatous components were not identified initially.

Various theories have been suggested for secondary melanoma in GCTs, like transformation of dermal elements, de-differentiation of germ cells to melanocytic neoplasia or even respiratory epithelium metaplasia. However, none has been proved till date.⁶ A secondary melanoma in teratomatous lesions originates at the dermo-epidermal junction similar to a cutaneous melanoma. It may also be derived from meningeal or uveal tissue within the teratoma. Other differentials for PMGCT with secondary melanoma include melanotic paragangliomas, schwannomas, carcinoids and even benign or atypical nevi, all of which are usually easily differentiated on immunohistochemistry.⁷

Vemurafinib has been approved for BRAF mutation positive stage IV melanoma. We checked BRAF mutation status, which was wild type in our case as well as in the previous case report. Literature search revealed that BRAF mutation is commonly present in melanomas of cutaneous origin while incidence at other sites is only 10-15%. Pertinent to these findings, our case did not harbour a BRAF mutation.⁸ Other newer agent for stage IV melanoma is Ipilimumab which has shown responses in approximately 20% of patients, although the responses are slow to occur, but once they occur they remain durable.⁹

Melanomas arising at unusual sites are generally

associated with poor prognosis than cutaneous primary.¹⁰ In our case, we think that melanoma cells did not respond to first-line chemotherapy as none of the BEP agents are active against melanoma. Moreover, it inherently has shown poor responses to chemotherapy. Traditionally, metastatic melanoma has a median survival of 9 months, which has recently been improved with use of targeted agents. However, 3-year overall survival remains well below 30% with both of these agents.¹⁰

Conclusion

Secondary melanoma in GCTs, especially in PMGCT, is rare with little information about its natural history. Primary cutaneous melanoma at other places should be ruled out before making a diagnosis of secondary transformation. In the absence of clear guidelines in this scenario, treatment recommendations for the primary cutaneous melanoma may be followed.

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