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Case Report

A Rare Case of a Germ-Cell Tumour Associated with Acute Megakaryoblastic Leukaemia- An Autopsy Report with Review of Literature

Dr. Gurpreet Kaur[1*], Renu Madan[2], Raghav Sharma[3], Arijit Sen[4]

[1]Department of Haemtopathology, AIIMS, New Delhi, India, 110029, **https://orcid.org/0000-0003-3535-4397**
[2]Department of Laboratory Sciences, Venkateshwar Hospital, New Delhi, India-110075, **https://orcid.org/0000-0002-5301-4591**
[3]Armed Forces Medical College, Pune, Maharashtra, India -411040, **https://orcid.org/0000-0002-7773-8869**
[4]Armed Forces Medical College, Pune, Maharashtra, India- 411040, **https://orcid.org/0000-0001-8473-0200**

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***Corresponding author:** Dr. Gurpreet Kaur
Department of Haemtopathology, AIIMS, New Delhi, India, 110029

Abstract

His association of mediastinal germ-cell tumours (MGCTs) with haematologic neoplasms is a rare though well known circumstance, and few cases are found in the literature. Most of these are non-seminomatous tumours in young males. The diagnosis of the haematological condition is usually either synchronic or metachronic with that of the germ-cell tumour. The prognosis is poor and basically determined by the haematologic neoplasia. Less than 20 cases of PMGCT with evolution into acute megakaryocytic leukemia have been reported in worldwide literature. Hematologic neoplasias associated with extragonadal germ cell tumors represent one of the most intriguing and biologically distinctive aspects of male germ cell cancers. The case report we present is that of a young 33 year old male with an initial diagnosis of both conditions which were detected synchronously. Despite timely intervention he succumbed to multiorgan failure following chemotherapy and an autopsy was performed.

Keywords: Germ cell tumours, Teratoma, acute megakaryoblastic leukaemia.

INTRODUCTION

Primary mediastinal germ cell tumors (PMGCTs) account for 1%–4% of all mediastinal tumors, very rarely are these associated with leukemias. A number of hematologic disorders have been found to be associated with mediastinal germ cell tumors, including acute megakaryocytic leukemia (M7), acute monocytic leukemia (M5), malignant tissue cell disease, and acute myelomonocytic leukemia (M4). Acute megakaryocytic leukemia is the commonest hematologic malignancy associated with PMGCT and so far, less than 27 cases of PMGCT with evolution into acute megakaryocytic leukemia have been reported in the literature. Due the relatively rare occurrence of this association, and absence of specific genetic, clinical, or other confirmatory test, the debatable etiology and the poor prognosis it portends these cases poses significant clinical challenges in diagnosis and management. We hereby present the salient autopsy findings of a 33 yr old male who presented with a concurrent PMGCT and an acute megakaryoblastic leukaemia.

CASE REPORT

A 33 year old male presented with a 3-week history of chest discomfort, breathlessness, and pleuritic chest pain. He had no history of associated comorbidities. His initial evaluation was normal genital examination. The initial laboratory workup showed polymorphonuclear leucocytosis (TLC-14,300/mm^3 reference range [RR] 4000-1200/mm^3) with thrombocytopenia (platelets of 60,000/mm^3, RR; 150,000-450,000/mm^3) serum lactate dehydrogenase (LDH) levels (234 IU/L, RR; 140-280 IU/L). The chest radiography showed a well defined radio-opaque mass in the mediastinum to the left with a wavy outline. The testicular ultrasound was unremarkable. The serum tumour markers were also increased; Alphafeto protein (AFP)-641.23 ng/ml (RR; 0-9ng/ml) and beta and beta-human chorionic gonadotrophin (BHCG) of 58.9mIU/ml (RR; non pregnant –0-5mIU/ml). The contrast enhanced CT thorax showed an anterior mediastinal mass lesion of (82x72mm in axial plane with 84mm in the coronal plane) predominantly compressing the arch of aorta and left main pulmonary artery and the inferior pulmonary vein. The whole body

PET CT scan showed a large mass lesion with heterogeneous FDG uptake measuring (82.3 x 110.0x 92.9mm) in the same site. An ultrasound guided trucut biopsy of the mass was done and was opined as a teratoma.

Meanwhile, the patient continued to have thrombocytopenia, and his peripheral blood smear revealed blasts with high nucleocytoplasmic ratio, sieve-like chromatin & 1-2 nucleoli (Figure 1(A) with peripheral blebbing of the cytoplasm consistent with a megakaryocytic differentiation. A subsequent bone marrow aspiration & biopsy were done. The aspirate was grossly haemodilute, the biopsy showed hypercellular areas with large atypical cells (Figure 1(B). Multiparametric flowcytometric analysis of the bone marrow aspirate showed CD 61 positive blasts suggestive of megakaryocytic lineage with normal lymphoid and myeloid series. Based on these findings he was managed as a case of mediastinal germ cell tumour with acute megakaryoblastic leukemia (AML M7). He was treated with two cycles of Bleomycin, Etoposide ,Cisplatin [BEP] regime followed by induction chemotherapy with Daunorubicin and Cytosine-Arabinoside (7+3 regime) .However, he developed febrile neutropenia after induction chemotherapy, and on day two of therapy he succumbed to his illness after 45 days of the, diagnosis.

AUTOPSY FINDINGS

After a mid-line incision the body was opened, a soft to firm variegated mediastinal mass measuring 30.3x10.5x7 cm was seen adherent to the left lung, abutting the heart (Figure 2A and 2B). Multiple small nodes measuring upto 1.5 cm were found in the perinephric fat of both kidneys and in the mesentry. The liver weighed 2000g (RR; 1100g-1600g) the spleen weighed 1000g (RR; 100g-150g). The cut surface of the liver appeared essentially unremarkable, the spleen was however congested. Multiple coronal sections of the brain showed areas of tiny punctate hemorrhages in the white matter of the right temporal, the right frontal, and occipital regions. The microscopy of the mediastinal mass showed discohesive cells lying in an alveolar pattern. These atypical bizarre hyperchromatic cells had vacuolated cytoplasm, irregular nuclear borders, and prominent nucleoli. Adipose tissue, specs of calcification, and glandular structures lined by stratified columnar epithelium and eosinophilic secretions were seen with extensive areas of necrosis and hyalinization (Figures 3 and 4A-4D).

On further microscopy, metastatic deposits of the mediastinal tumour cells were seen in the brain, spleen, bone marrow perinephric fat, and in the mesentery. Lungs showed features of acute respiratory distress syndrome while kidneys showed features of acute kidney injury. The testis was essentially unremarkable. The cause of death was reported out as multiorgan failure with acute lung injury and acute kidney injury with metastatic mediastinal germ cell tumour along with acute megakaryoblastic leukemia.

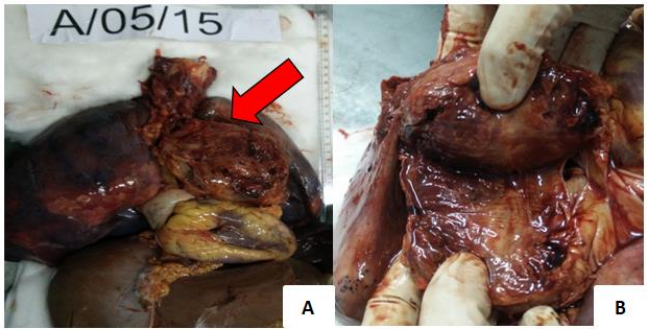

Fig 1(A-B): A firm to soft variegated mass in the mediastinum which was abutting the heart, measuring 10.7x10.3x7cm

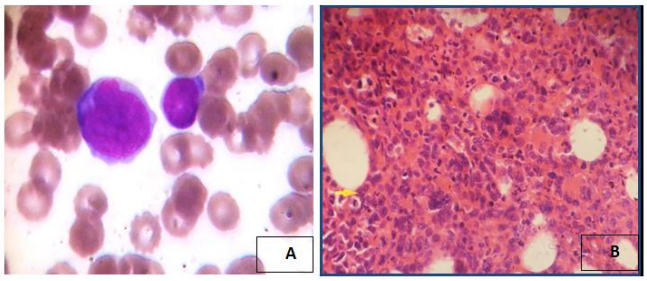

Fig 2(A): Blasts are medium sized with blue vacuolated, agranular, eosinophilic cytoplasm containing fine granules, cytoplasmic projections in the form of blebs and pseudopods resembling platelets with irregular cytoplasmic borders. The Nuclei are round or slightly indented with finely reticular, dense chromatin and 1 - 3 nucleoli 2.(B) Bone marrow biopsy revealing proliferate of atypical megakaryocytes

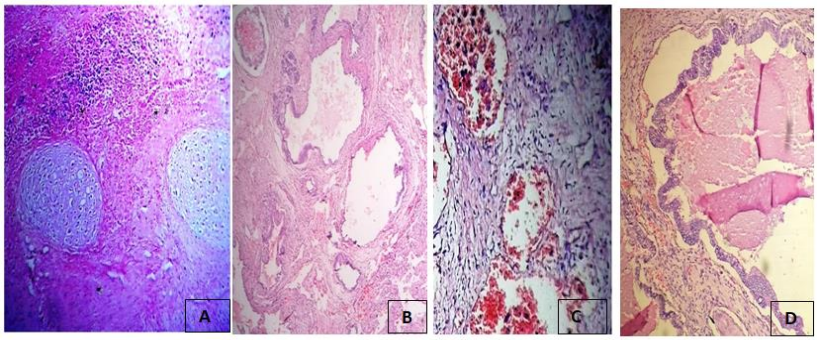

Fig 4(A-D): Elements form all three germ layer including (A) Cartilage (B) columnar glands (C) blood vessels (D) squamous elements e

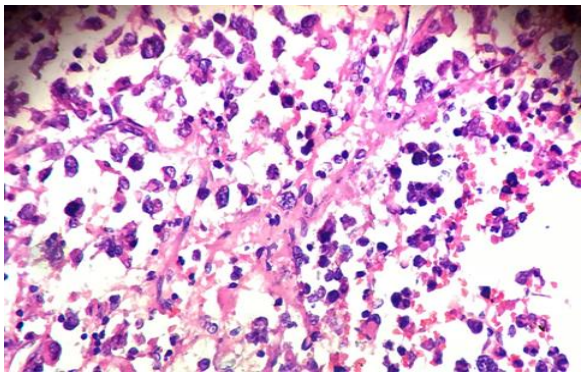

Fig 5: Cells from the tumour which were dischohesive and lying in an alveolar pattern

DISCUSSION

Germ-cell tumours (GCTs) account for 2% of human malignancies and are the most common malignant tumors in males aged 15-35. The association between MGCT and acute megakaryoblastic (M7) leukemia has become well known since the first case in 1985 [1, 2]. These tumors may arise synchronous or metachronous with acute myeloid leukaemia [3]. The overall incidence of leukemia in patients with mediastinal non-seminomatous germ cell tumors is estimated to be 5.9% [4]. The theory of multipotent differentiation of malignant germ cells in such cases is supported by cytogenetic analysis where isochromosome 12p [i(12p)] is frequently seen. Besides acute megakaryoblastic leukemia other hematological malignancies like acute monocytic leukemia, malignant histiocytosis, myelodysplastic syndrome, and acute myelomonocytic leukemia have been associated with mediastinal germ cell tumors. The most common leukemia that occurs with MGCT is, however, AML-M7, as was the case of our patient.

In a large series of 26 cases by Mukherjee *et al*., [4] the median age was 24 years (range 13 to 36 years) and these were seen more frequently in males. All cases of MGCT were of non-seminomatous origin. MGCT occurred prior to the diagnosis of leukemia in 46% of cases and concomitantly in 31% of the cases. The median time from diagnosis of MGCT to the development of M7 leukemia was 5 months (range 2.25 to 39 months) and the median time to death from the initial diagnosis of MGCT was 6 months (range 0.5 to 60 months). Only one case was successfully treated with an allogenic stem cell transplant for the M7 leukemia [4].

Hematologic disorders associated with primary mediastinal germ cell tumors have to be distinguished from therapy related secondary leukemia. Leukemias associated with the use of alkylating agents usually occur after an average interval of 5–7 years, often preceded by a preleukemic period of myelodysplasia (MDS) and frequently progressing to AML, while those with topoisomerase II inhibitors occlude post a shorter latency period and are usually not preceded by an Myelodysplastic syndrome like picture [2].

The clinicopathological features of these tumors may vary from gonadal and retroperitoneal germ cell tumors and they often contain a yolk sac component. They often contain areas of yolk sac tumor that has a mesenchyme-like pluripotent component. Teratomas containing all the three germ layers with varying degrees of differentiation is derived from a malignant precursor cell which as being totipotent is able to differentiate into non germinal tissue. These have frequently been seen to harbor malignant transformation [5].

Studies by Hartman *et al*., [4] showed that the most common karyotype abnormality of the germ cell tumors was i(12p), in 38% of patients while trisomy 8 and Klinefelter's syndrome were also seen in 16% and 14% respectively. The clonal relationship between a mediastinal germ cell tumor and acute myelogenous leukemia has been supported by various studies including those by Ladanyi and Woodruff [6, 7].

In the series by Ladyani [6] one patient had i(12p) in his germ cell tumor and in the leukemic blasts, a second patient had evidence of i(12p), and in a third patient, the leukemic cells co-expressed myelomonocytic antigens (My4, and HAM56, My9) and cytokeratin which suggested both myeloid and germ cell differentiation. In the study by Orazi [5] both

blasts and erythroblasts were seen in the germ cell component expressing CD34, myeloid any erythroid markers such as CD71. They also had a higher expression of p53, which is unusual in acute leukemias but common in MGCTs. The cytogenetic and molecular biologic findings of these studies, therefore suggested a common progenitor for the hematologic malignancy and the MGCT.

A variety of treatment modalities can be used to treat MGCT as well as the leukemia; of these surgical resection and platinum-based chemotherapy are the mainstay treatment and they have been used in variable series of MGCT [4, 5]. The AML component has traditionally been treated with either anthracycline or cytarabine-based induction chemotherapy. Since the overall prognosis for such patients is very poor, an allogenic transplant may be considered at first remission in few select cases [5, 9, 10].

In summary, patients with a history of mediastinal germ cell tumors are at higher risk of developing acute leukemias. These patients should, therefore be kept under long term follow up. In spite of the significant advances in chemotherapy, the prognosis is such patients remains bleak, and allogenic stem cell transplantation may be considered.

Extended insights into the biology of this disease association and improved strategies to treat hematologic disorders in primary mediastinal nonseminomatous germ cell tumors should be areas of further investigation.

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