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Concurrent mediastinal germ-cell tumour and haematological malignancy: Case report and short review of literature

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Germ-cell tumours (GCTs) account for 2% of human malignancies, but are the most common malignant tumours in males aged 15–35. Approximately 2–5% of the GCTs arise at extragonadal sites, usually in the midline of the body, with the mediastinum and retroperitoneum as the two major sites (54 and 45% of the cases, respectively) [1]. Garnick et al. reported an association between haematological malignancies and mediastinal GCTs in 1983 [2] and several cases have been published since [3–8]. The majority present with a mediastinal GCT and develop the haematological malignancy several months later, with a median interval of 6 months between the two diagnoses [8]. We report three cases in which the haematological malignancies were concurrent with the mediastinal GCTs.

Case 1

A 31-year-old male presented with fatigue, fever, weight loss, night sweating, and diffuse muscular pain. The investigation revealed anaemia, thrombocytopenia, and a mediastinal tumour (Table I). Bone marrow trephine biopsy and aspirate showed acute megakaryoblastic leukaemia (M7) (Figure 1a), whereas a mediastinal biopsy showed a GCT with embryonal carcinoma, endodermal sinus tumour, and mature teratoma components. The serum levels of alpha-fetoprotein (AFP) and human chorion gonadotropin (HCG) were elevated (Table I). An ultrasound scan of the testicles with subsequent biopsies demonstrated bilateral leukemic infiltrates. The patient showed a partial response on cisplatin based chemotherapy and intrathecal chemotherapy (Table I). Five months following diagnosis, however, he developed disease progression with pancytopenia and died due to an acute gastrointestinal bleeding.

Case 2

A 25-year-old male presented with fatigue, fever, cough, and chest pain. The investigation showed anaemia, elevated leukocyte and platelet counts, and a mediastinal tumour (Table I). Bone marrow aspirate and trephine biopsy were compatible with malignant histiocytosis. Fuorescence *in situ* hyridization (FISH) analyses demonstrated the presence of the GCT specific marker isochromosome 12p (i12p). The mediastinal tumour was a GCT with mature and immature teratoma components. AFP and HCG levels were elevated (Table I) and bilateral biopsies from atrophic testicles showed atypic cellular infiltrates, most likely leukemic. The patient received a single course of cisplatin based chemotherapy, but developed septicaemia and an acute respiratory distress syndrome and died less than a month following diagnosis.

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Table I

	Patient 1	Patient 2	Patient 3
Time of diagnosis	June 1995	December 2001	June 2003
Age of onset (years)	31	25	27
Haematology			
Hb (g/dl)	8.2	10.8	5.2
Leukocyte counts	5.5×10^9	30.2×10^9	2.6×10^9
Platelet counts	15×10^9	789×10^9	24×10^9
Tumour markers			
AFP (μg/l)	329 (<13)	23 151 (<13)	171 (<13)
HCG (μg/l)	67 (<5)	13 (<5)	26 (<5)
LD (U/l)	30 000	2360	184
Histology of the mediastinal tumour	Germ-cell tumour with embryonal carcinoma, endodermal sinus tumour, and mature teratoma components	Germ-cell tumour with mature and immature teratoma components	Necrotic carcinoma compatible with teratocarcinoma
Bone marrow trephine biopsy/Aspirate	Dry tap Acute megacaryoblast leukaemia (M7)	Malignant histiocytosis Isochromosome12p	Malignant histiocytosis with haemophagocytosis
Testicles	Leukemic infiltrates	Testicular atrophy Leukemic infiltrates	Hypoeccoic lesion Focal infiltration of histiocytosis
Chemotherapy	4 BEP (bleomycin, etoposide, cisplatin)/intrathecal methotrexate, cytarabin, and methylprednisolone	BEP	PAI (cisplatin, doxorubicin, ifosfamide) + 3 BEP
Survival	6 months	1 month	5 months

Case 3

A 27-year-old male presented with fatigue, breathlessness at exertion, dizziness, cough, and chest pain. The investigation revealed anaemia, pancythopenia, and elevated AFP and HCG-levels (Table I). Bone marrow trephine biopsy and aspirate showed malignant histiocytosis with haemophagocytosis (Figure 1b). CT-scans demonstrated a large mediastinal tumour and lung, liver and spleen metastases. Small biopsies from the mediastinal tumour contained a partially necrotic carcinoma, compatible with teratocarcinoma. No other tumour components were seen. Based on the elevated tumour markers, the mediastinal tumour was considered most likely a nonseminomatous GCT. There were small hypoeccoic lesions in the left testicle which was removed and turned out to harbour focal infiltration of malignant histiocytosis (Figure 1c and d). The patient received four courses of cisplatin based chemotherapy (Table I). The disease, however, progressed and the patient died five months following diagnosis.

Discussion

The three cases support previous evidence of an association between haematological malignancies and mediastinal GCTs in young males. A total of 64 cases have been published [2–8]. The syndrome seems to be specific for mediastinal nonseminomatous GCTs, and frequently there are serologic (elevated AFP) or histologic evidence of yolk-sac elements [5,8]. It should be noted however, that there are two reports in which the GCTs were located in the testicle and in the midline of the brain, respectively [9,10]. One of the three present patients suffered from acute megakaryoblastic leukaemia, the two others from malignant histiocytosis. These two, otherwise rare, diseases previously have been reported to be the most common haematological neoplasias in this syndrome [5].

Haematological malignancies associated with nonseminomatous mediastinal GCTs have to be distinguished from therapy-related secondary leukemias. Leukemias caused by alkylating agents or topoisomerase II inhibitor, typically are diagnosed 5–7 and 2–3 years following therapy, respectively [8]. The fact that the present three cases presented with haematological malignancy before instalment of any treatment, excludes the possibility that the haematological malignancies were therapy-related. In previous reports 5/16 and 2/17 patients with haematological malignancy and EGCT presented simultaneously with the two diagnoses [5,8].

Nonseminomatous GCTs have the capacity to display totipotential differentiation, ranging from pluripotential embryonal carcinoma to extraembryonic or somatic cell types (teratomas). On rare occasions teratomas undergo malignant transformation into somatic components indistinguishable from primary malignancies like sarcoma or adenocarcinoma. Accordingly, the hematologic malignancies may well represent malignant transformation of hematopoietic tissue within the EGCTs. Supporting this hypothesis is the fact that the GCT-specific

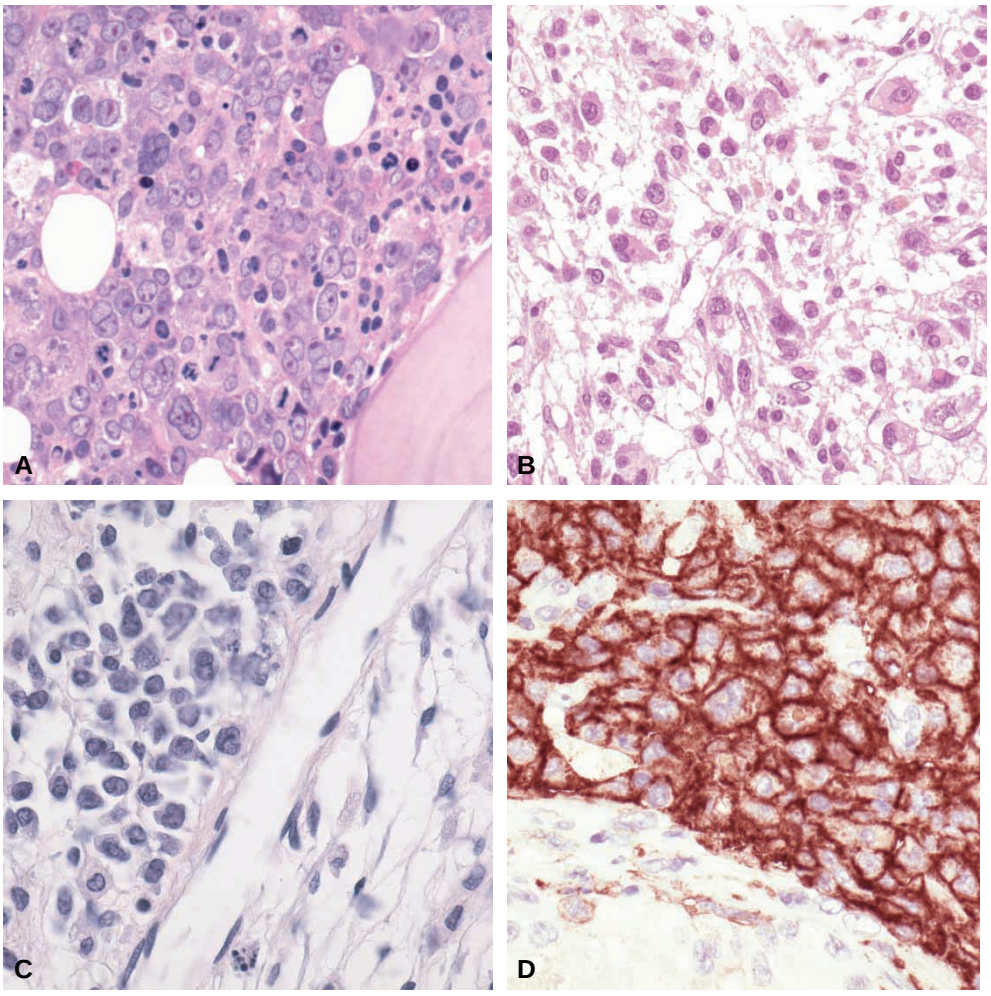

Figure 1. A. Patient 1. The bone marrow trephine biopsy shows massive infiltration with megakaryoblasts (HE stain, 200 ×) B. Patient 3. The bone marrow shows infiltration with atypical histiocytic cells. Edema is noted in the background (HE stain, 200 ×) C. Patient 3. The testis biopsy shows interstitial infiltration with atypical histiocytes (HE stain, 300 ×). D. Patient 3. The atypical infiltrate in the testis expresses the monocyte-histiocyte marker CD14 (immunoperoxidase stain, 300 ×).

cytogenetic marker i(12p) was found in the bone marrow of patient 2 and in a few previous reported cases [9,11,12].

All of the three patients had an aggressive clinical course of the disease and died within 6 months of diagnosis, in spite of cisplatin-based chemotherapy directed towards the GCT. In a previous report on 17 patients treated with cisplatin-based regimens, none were alive following two years of observation [8]. Chemotherapy against teratomas with malignant transformation into nonhaematological neoplasms usually is dictated by the transformed histology. Therapeutic regimens should be designed to target the haematological malignancy as well as the GCT.

Our report underscores the importance of screening young males with haematological malignancies, especially with rare subtypes thereof, such as megakaryoblastic leukemia or malignant histiocytosis, for mediastinal GCTs. This can easily be accomplished by determining serum AFP and HCG and by performing radiological examination of the thorax. *Mutatis mutandis*, it seems reasonable to propose that bone marrow aspirate and trephine biopsy should be taken in all patients diagnosed with mediastinal nonseminomatous GCTs.

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Childhood papillary thyroid cancer as second malignancy after successful treatment of rhabdomyosarcoma

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To the Editor,

Second malignant neoplasms are a major concern during the long-term follow-up of paediatric patients after successful multi-modality treatment. The only pathogenic factor known to promote development of thyroid cancer in children is radiation, which induces activating rearrangements in the *RET* gene [1–3].

An eighteen month old boy presented with a large intrathoracic paraspinal mass invading the lower thoracic vertebrae causing spinal cord compression. He had no congenital abnormalities, developmental delays, history of antenatal exposure to radiation or other carcinogens, nor any family history of benign thyroid conditions or malignancy. Haematological examination, bone marrow studies, Serum Alfa-fetoprotein, Human Chorionic Gonadotrophin, urinary Vanillyl-Mandelic Acid, Homo-Vanillic Acid and Dopamine levels, Tc^{99} MIBG and bone scan were normal. Biopsy from the tumor showed an undifferentiated malignancy composed of small round blue cells with scanty cytoplasm and extensive stroma with necrosis within fibrosis. FISH showed FKHR disrupting translocation, with no EWS disruption. Final diagnosis was Embryonal Rhabdomyosarcoma.

Chemotherapy (International Society of Paediatric Oncology – malignant mesenchymal tumour (SIOP-MMT) 95 protocol) with a six drug schedule (Ifosfamide (cumulative dose – 18 480 mg), Vincristine (10.92 mg), Carboplatin (840 mg), ActinomycinD (2.52 mg), Epirubicin (840 mg) and Etoposide (1 176 mg)), was given for 9 cycles resulting in a radiologic partial response. Thoracotomy and resection of the paraspinal residual tumor revealed a pathological complete response. The patient did not receive adjuvant radiotherapy and was on regular follow-up with normal growth and development. Three CT scans of the thorax were performed during diagnosis, treatment and follow-up.

Six years after completing treatment, a non tender thyroid swelling was detected on follow-up. Ultrasound scan showed a vascular nodule in the left lobe

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