Reminder of important clinical lesson

Malignant transformations in a patient with a mediastinal germ cell tumour: lack of efficacy of bone marrow transplantation after chemotherapy on tumour recurrence

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Summary

The report describes the case of a young male with a malignant teratoma which was followed by an acute megakaryoblastic leukaemia sharing similar chromosomal abnormalities. In leukemic cells, the authors have obtained cytogenetic evidence by fluorescent in situ hybridisation technique suggesting that this leukaemia arose directly from the germ cell tumour (GCT). The patient received allogenic bone marrow transplantation, which unfortunately, did not prevent the patient to relapse with an undifferentiated sarcoma containing rhabdomyosarcoma components, as well as reappearance of a residual teratoma with metastasis. The treatment strategy for malignant transformation of a GCT seems to be unpredictable and should be dictated by the malignant tissue counterpart. Except for acute leukaemia, unresectable or metastatic settings will generally require multi-modal therapy including chemotherapy, in addition to loco regional approaches. Additionally, long or even a life time follow-up is necessary in patients with poor prognostic characteristics.

BACKGROUND

I would like to share this case report because of its informative quality. Only three similar cases have undergone bone marrow transplantation (BMT).

Our case report points out the importance of delineation of germ cell tumour (GCT) prognostic factors that enables better management. Additionally, this report confirms the importance of complete resection in such tumours, and therefore better outcome.

CASE PRESENTATION

A teenage boy presented with a 3 week history of chest pain, cough and rapidly progressing orthopnea and slight dysphagia.

The examination revealed a splenomegaly of 1 cm below the costal margin and a left-sided axillary lymph node (1.5 cm), but no alteration in the general condition and no abnormality of the respiratory sounds. The respiratory saturation was of 100% in normal breathing conditions.

INVESTIGATIONS

Radiographic examination showed a soft tissue mediastinal mass located anteriorly measuring 17×7 cm (figure 1). MRI revealed that the mass arose near the thymic lobe and appeared to be responsible for right atrial compression, dilatation of the inferior vena cava, compression and dilatation of the superior vena cava. The high levels of α fetoprotein (566 ng/ml) and β -human chorionic gonadotropin (β -HCG) (2.6 IU/l) confirmed the diagnosis of non-seminomatous germ cell tumour (NSGCT). No abnormality was

observed on the abdominal ultrasound and the blood picture was normal.

TREATMENT

The patient received two courses of chemotherapy according to the French protocol TGM 95 for extracerebral malignant GCTs in children, which included vinblastine, bleomycin and cisplatin. However, the mass increased in size by 2 cm in all axis and there was only a slight reduction in the level of α fetoprotein with normalisation of

Figure 1 Chest x-ray shows a soft tissue mediastinal mass.

Figure 2 Karyotype of the leukemic cells shows similar chromosomal abnormality of trisomy 7 and 8 found in teratomatous cells.

β -HCG level. A microscopically incomplete resection was performed. There was no invasion to the thymic matter. Histologically, the mass was a teratoma composed of mature and immature areas. No cytogenetic analysis was performed on fresh tissue. The patient received three additional courses of chemotherapy.

OUTCOME AND FOLLOW-UP

Four months later, the patient presented with rapidly progressing thrombocytopenia, weight loss and moderate splenomegaly. No lymphadenopathy was found. The complete blood picture showed a pancytopenia (haemoglobin 8.4 g/dl, white blood cell 2400/mm³, platelets 20 000/mm³), blood smear showed 21% blast cells which were positive for CD41, CD42 and CD61. Bone marrow biopsy and aspiration revealed a partial infiltration with 6.5% of abnormal undifferentiated cells with diminished megakaryocytes. On immunological phenotyping, these cells were CD117+, CD42b+, CD41+, CD61+ but factor 8 -, CD163- and tryptase -. The karyotype analysis revealed the presence of hyperdiploidy without any translocation (figure 2).

According to the French American British (FAB) classification, the diagnosis of secondary subacute myeloid leukaemia type 7 was made. The patient was treated with chemotherapy according to the French protocol ELAM 02 for acute myeloid leukaemia. The patient was in complete remission after a course of cytarabine (200 mg/m²/day $\times$ 7 days) and mitoxantrone (12 mg/m²/day $\times$ 5 days). Then he received two courses of consolidation based on cytarabine and amsacrine, followed by cytarabine, etoposide and daunorubicine. An unrelated human leucocyte antigen identical BMT was carried out, after a conditioning regimen consisting of intravenous busulfan (0.8 mg/kg every 6 h for 4 days; d-10 to d-7), cyclophosphamide (50 mg/kg/day for 4 days; d-6 to d-3) and antilymphocyte serum (5 mg/kg/day for 4 days). A haematological recovery was rapidly obtained (platelet >50 000 / μ l at d 20, granulocyte >500/ μ l at d 30). No complication, related to the BMT was observed.

The patient remained in complete remission for 2 years post transplant and then he relapsed with a right-sided mediastinal undifferentiated sarcoma with a rhabdomyosarcoma component. A microscopically incomplete surgical excision was performed then the patient received 8 months of chemotherapy (ifosfamide, vincristin, actinomycin) followed by 50 grays of radiotherapy. Complete remission was re-achieved.

Approximately a year later, the patient was discovered to have a left-sided metastatic pulmonary nodule, which was found, after excision, to be a teratoma with a major epithelial component. Another left-sided thoracic relapse with lymphadenopathy occurred 6 months later. The patient died from tumour progression 5 years after the diagnosis and 3 years 8 months after the BMT without relapse of the leukemic transformation

DISCUSSION

Malignant transformation can occur in GCT from any primary site, but they arise more commonly from the mediastinal NSGCT than from other sites.¹ Such malignant transformation of teratomas, occurring in 3–6% of patients, leads to aggressive malignancies displaying histologic differentiation along variable histological lineages such as sarcomas, leukaemia, carcinomas and primitive neuroectodermal tumours.²

The association between mediastinal GCT and haematological malignancies was first recognized in 1985.³ These haematological malignancies show a high incidence of rare phenotypes of acute myeloid leukaemia (acute myelomonocytic or megakaryoblastic leukaemia), and less frequently, malignant histiocytosis, erythroleukemia or essential thrombocythemia. Moreover some of these developing leukaemias do not fit the categories of the FAB classification, and are usually associated with extremely poor prognosis.^{4,5}

Biologically speaking, literature reports have suggested that the presence of highly non-random chromosomal abnormalities as isochromosome (12p), trisomy 8 and +X, with or without constitutional Klinefelter's syndrome, in patients with microinvasive germ cell tumour may be associated with leukaemia.^{6,7} In our patient, the absence of i(12)p amplification and an additional X chromosome, supported that they may not be a prerequisite for development of GCT-related haematological malignancies. The finding of i(12)p in a tumour karyotype should not be interpreted as conclusive evidence of a germ cell origin of the neoplastic disease.⁸ Nevertheless, in our patient cytogenetic examination demonstrated the presence of a similar clone abnormality in both the specimen of GCT and leukaemia (figure 3); this clone abnormality was not searched in the rhabdomyosarcoma lesion developed afterwards. Moreover, morphological similarities were observed between the unidentified cells present in the teratomatous lesion and the abnormal cells in the bone marrow after development of acute leukaemia. Experimental

Figure 3 (A–C) Histological section of mediastinal germ cell tumour analysed by fluorescent in situ hybridisation technique showing chromosome 7 in red and chromosome 8 in green. A chromosome 7 and 8 trisomy is observed in cells located in an atypically differentiated region (arrows).

data that have been reported support the hypotheses of early progenitor leukemic cell differentiation within the yolk sac component of mediastinal NSGCT before homing in the bone marrow.⁹

Malignant transformations of GCT can arise both before and after chemotherapy, indicating that chemotherapy is unlikely the cause of this transformation. So the most challenging tasks are how to predict that a certain patient has the liability to develop a malignant transformation and how to prevent it.

Recently the International Germ Cell Cancer Collaboration Group considered that the presence of a primary mediastinal site in patients with NSGCT is an adverse factor which is associated with lower remission rates and a high rate of relapse with failure of chemotherapy.¹⁰

Treatment resistance is substantially more frequent in tumours with an abnormal karyotype, so that new treatment strategies are required for patients who fail to achieve complete remission.¹¹ In our patient, the potential therapeutic impact of allogeneic BMT was seen to be favourable for the leukemic transformation but this procedure was unable to purge the patient from residual malignant cells initiating a secondary sarcoma and then a relapse of the immature teratoma. However, Goodwin *et al* reported a patient with a long-term survival after a treatment with allogeneic BMT, suggesting a possible benefit of a graft versus tumour effect for their patient with relapsed GCT.¹² Whereas Hiramatsu *et al* reported in a Klinefelter's patient, a mediastinal GCT and leukaemia treated with a BMT but did not observe any regression of the initial teratoma and proceeded to complete surgical resection of the mediastinal tumour.¹³

Our case report points out the importance of delineation of GCT prognostic factors that enables better management and therefore better outcome. Unfortunately attempts to tailor the treatment strategies to the histological characteristics of the presenting tumour were not able to eradicate the primitive malignant cells from relapsing. Thus initial complete resection is critical to prevent subsequent secondary tumours and relapses.

Learning points

- Concentration on the importance of complete surgical resection of the initial GCT, whatever the therapeutic strategy proposed later.
- The treatment strategy for malignant transformation of a GCT seems to be unpredictable and should be dictated by the malignant tissue counterpart. Except for acute leukaemia, unresectable or metastatic settings will generally require multimodal therapy including chemotherapy, in addition to loco regional approaches.
- BMT could not prevent, in this case, the tumour relapse.
- Additionally, long or even a life time follow-up is necessary in patients with poor prognostic characteristics.

Competing interests None.

Patient consent Not obtained.

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