

Primary malignant germ cell tumours

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Citation

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Abstract

Study objectives : the aim of this enquiry was to perform a retrospective review on patients treated for primary malignant mediastinal germ cell tumours (PMMGCT) between 1992-2008, to specify their clinical characteristics, their prognostic factors and to evaluate the current therapeutic strategies. Patients: we report a study about 8 patients with seminoma in 3 cases, yolk sac tumour (YST) in 2 cases, embryonal carcinoma (EC) in 1 case, choriocarcinoma in 1 case and teratocarcinoma in 1 case. Pathologic diagnoses were confirmed in all cases by surgical biopsy and a resection of the residual mass in 2 cases. Results: all the patients were male with a mean age of 32 years (range, 16 to 63 years). Only one patient was asymptomatic. The most frequent symptoms were cough (87.5%), chest pain (50%) and dyspnea (50%). The 8 tumours were located in the anterior mediastinum. One patient with EC didn't received any treatment because of the rapid evolution of the disease. The 7 others received pre-operative chemotherapy and 3 patients received a second-line chemotherapy because of the persistence of viable tumours in one case (YST) and a resistance to the first chemotherapy in 2 cases (seminoma and teratocarcinoma). The overall 2-year survival of patients with seminoma was 100% towards 25% for those with nonseminomatous tumours. The patients with stage I disease survived for a mean period of 3 years. Conclusion: The PMMGCT cause generally a diagnostic challenge because of the difficulty of their resection and the little size of the biopsy specimen. Besides, the absence of a primary gonadal localization may be difficult to establish. These tumours have a worse prognosis than their gonadal counterparts. Prognostic factors are multiple and not accurate. The most relevant ones seem to be the histological type and the disease stage.

INTRODUCTION

The primary malignant mediastinal germ cell tumours (PMMGCT) are a rare tumours affecting usually young men (1). These tumours are generally located in the anterior mediastinum. They account for 1 to 6% of all mediastinal tumours and 1 to 2% of all germ cell tumours (GCT) (2, 3, 4, 5). Their definition necessitates the absence of a primary gonadal GCT which must be explored.

MATERIAL AND METHODS

A retrospective review of medical records was performed on patients who were treated for PMMGCT between march 1992 and march 2008. Inclusion criteria were (1) anterior MMGCT (2) No evidence of GCT in the testis (3) a diagnosis of MMGCT by biopsy or curative resection. Routine evaluations included chest and abdominal computed tomography, testis sonography and tumour marker study including serum levels for α -fetoprotein (α FP) and β - Human chorionic gonadotrophin (β - HCG). Pretreatment pathologic diagnoses were confirmed in all patients by surgical biopsy and a study of a resected mass in 2 cases. Preoperative

chemotherapy was administrated to 7 patients and surgical extirpation of residual mass was performed in 2 cases. Three chemotherapy regimens were used for first-line chemotherapy: bleomycin, etoposid and cisplatin (BEP) for 3 patients, etoposid, ifosfamide and cisplatin (VIP) for 3 patients, cisplatin, vinblastin, etoposid, bleomycin (PVeVP) for 1 patient. The mean number of chemotherapy regimen cycles delivered was 4 (range, 3 to 6 cycles). The mean period of follow up was 24,6 months (range, 1 to 48 months). No statistical test was used because of the number of cases studied.

RESULTS

During this period, 470 mediastinal tumours were diagnosed on biopsies (through mediastinotomy or mediastinoscopy) or on resected masses. Malignant GCT accounted for 1,6% of all these mediastinal tumours. Our 8 MMGCT comprised 3 seminomas, 2 yolk sac tumours, 1 mixed GCT, one choriocarcinoma and 1 embryonal carcinoma. Tumour cell types are listed in Table 1.

{image:1}

All the patients were male with a mean age of 32 years (range, 16 to 63 years). Only one patient was asymptomatic. His tumour was discovered incidentally. The 7 other patients were symptomatic at diagnosis and the most frequent symptoms were cough in 7 (87,5%), chest pain in 4 (50%), dyspnea in 4 (50%) and deterioration of the general state in 4 (50%). Physical examination was normal in 5 patients. It showed signs in relation with a compression of the superior vena cava in 2 cases and sub-clavicular adenomegalies in 1 case. Tumour marker concentrations including β -FP and β -HCG were elevated in 4 patients. β -FP level was increased in 2 cases of yolk sac tumour and 1 case of mixed GCT. The β -HCG level was elevated in 1 case of choriocarcinoma. Imaging examination showed a mediastinal mass in all cases, with cystic components in 2 cases, tumoral calcifications in 1 case and a necrosis in 2 cases. The masses were located in the anterior mediastinum with extension to the middle mediastinum in one case (Figures 1, 2).

{image:2}

{image:3}

These masses reached a mean size of 11 cm (range, 8 to 16 cm). Many diagnoses were suspected according to the clinical and radiological findings. They consisted in a bronchogenic cyst in one case, a thymoma in one case and MMGC tumours in 7 cases. An extemporaneous examination was performed in 2 cases concluding to an undifferentiated malignant process without an accurate diagnosis. Surgical biopsy was performed in all patients. A resection of the residual mass was possible in 2 cases. In the first one, the histological examination confirmed the initial diagnosis performed through surgical biopsy. In the second case, the samplings enabled to discover another tumoral component consisting in a yolk sac tumour in addition to the first teratomatous component showed by the biopsy. So that the diagnosis of mixed GCT was retained. The histological findings were common in all cases. In seminomas, they showed round and clear tumour cells growing in a confluent and multinodular clusters through a prominent inflammatory background infiltrate of small mature lymphocytes, plasma cells and occasional eosinophils. The tumour cells showed round nuclei with one or more nucleoli. Immunohistochemically, 90% of the tumour cells were positive for PLAP (Figure 3).

{image:4}

The embryonal carcinoma was characterized by a solid growth pattern composed of large polygonal cells with indistinct borders and large and hyperchromatic nuclei (Figure 4).

{image:5}

All the tumour cells expressed CD30. The yolk sac tumours were composed of medium pale cells adopting a pseudopapillary appearance with many Schiller-Duval bodies. The tumour cells were positive for β FP in immunohistochemical study (Figure 5).

{image:6}

Choriocarcinoma was characterized by the presence of syncytiotrophoblasts and cytotrophoblasts growing in a plexiform pattern with a hemorrhagic and necrotic background. All tumour cells expressed pankeratin markers, additionally, the syncytiotrophoblasts react with β HCG (Figure 6).

{image:7}

The mixed GCT was made of 2 components: a teratomatous one and a yolk sac tumour expressing β FP. The staging of Moran, which was established in 1997 to classify the primary mediastinal GCT was used in all cases. The 8 tumours were classified in stage I in 3 cases, stage II in 3 cases and stage III in 2 cases. One patient with embryonal carcinoma didn't received any treatment because of the rapid evolution of the disease. The 7 other patients received an initial chemotherapy. The patients with seminoma received a radiation therapy in association to the chemotherapy. A surgical excision of the residual mass was possible in 2 cases. Three patients received a second-line chemotherapy because of the persistence of viable tumour cells in one patient with yolk sac tumour and the resistance to the initial chemotherapy in the 2 other cases. Two patients with seminoma and one with mixed GCT were free of disease after a mean follow up period of 3 years (range, 2 to 4 years). Three patients died. The first case of seminoma presented cerebral metastases 2 years after the first diagnosis. The second case of choriocarcinoma died during the initial chemotherapy. The third patient with embryonal carcinoma presented hepatic metastases. Two patients suffering from yolk sac tumours were lost of view with a regression of a disease in the first case and the appearance of medullary metastases in the second one. The patients' characteristics and outcome are listed in Table 2.

{image:8}

Pts : patients, CT : chemotherapy, SR : surgical resection, RT : radiation therapy, CP : chest pain, DGS : deterioration of the general state, ASMM : anteo-superior mediastinal mass, FOD : free of disease, CC : choriocarcinoma, VI : vascular invasion, YST : yolk sac tumour, AMMM: anterior and middle mediastinal mass, CI: cardiac invasion, RRM: resection of the residual mass, LOV: lost of view, GGS: good general state, EC: embryonal carcinoma, MGCT: mixed germ cell tumour, TK: tératocarcinome.

DISCUSSION

The classification of the World Health Organization distinguishes teratomas, which are usually mature and benign from nonteratomatous tumours that are always malignant. The latter ones are divided in seminomatous and nonseminomatous tumours (NST) (1). Seminomas derive directly from the gonocysts, in the other side, the nonseminomatous tumours derive from undifferentiated embryonal cells (yolk sac tumour, embryonal carcinoma, choriocarcinoma) (6). Generally, the malignant GCT are rarely pure. They usually contain many tumoral components. Their incidence varies in the literature from 33 to 100% (7, 8, 9, 10, 11, 12, 13, 14). In our study, the diagnosis was made on surgical biopsy in 5 cases and on the analysis of the resected mass in 2 cases. This fact may explain the rarity of the mixed GCT. Two theories have been proposed to explain the development of MMGCT. One is that MMGCT originate from germ cells that migrate during embryogenesis and the other theory is that they originate from germ cells that are widely distributed during embryogenesis (15). MMGCT are observed in men in 90% of the cases with a mean age of 30 years (1). Women are concerned in 4 to 10% of all cases (16). The yolk sac tumours are frequently reported in women. According to the literature, all our patients were men with a mean age of 33 years. In comparison with teratomas, which are usually asymptomatic, MMGCT are symptomatic in only 15 to 30% of all cases (17, 18). Besides, the clinical history depends on the histological nature of the tumour. 38% of the seminomas and 10% of the NST are asymptomatic (17). This may be due to the slow and silent evolution of seminomas in comparison with NST which are characterized by a rapid evolution with an extension to the adjacent organs. In opposition to the literature, in our study seminomatous tumours were symptomatic. In symptomatic patients, the cough, the dyspnea, the chest pain and the deterioration of the deterioration of the general state are the most frequent

symptoms. They reported respectively in 24%, 48%, 25% and 30% of the cases (17, 19). In 10 to 20% of the cases, the patients may present acute symptoms in relation with the compression of the superior vena cava (20). The metastases may also be present at first presentation or during the evolution of the disease in 35 to 95% of the cases (21, 22). They may be pulmonary, pleural, cerebral, hepatic etc. the tumor marker concentrations including α FP, β HCG and lactate dehydrogenase must be available before any therapeutic option. These markers present a diagnostic and a prognostic impact (1). Besides, they are necessary in the follow up of the patients. For some authors, the diagnosis of NST is dependent on these markers even if there's no histological confirmation of the diagnosis (23). 70 to 75% of the MMGCT are located in the anterior mediastinum (24, 25). Rare cases were reported in the posterior or middle compartments (26, 27). Imaging findings show usually a homogeneous mass in case of seminomas and a heterogeneous mass in case of NST (28). The accurate diagnosis remains based on histological findings especially when the tumour marker concentrations are normal. Surgical biopsies through mediastinotomy or mediastinoscopy are usually the only diagnostic means especially in these tumours which are usually difficult to extract. Nevertheless, these biopsies concern usually one tumoral component in case of mixed GCT or they may involve a necrotic tissue. So that, the extemporaneous exam is necessary to evaluate them. An accurate histological diagnosis necessitates a sampling of the tumour mass, but the surgical excision is possible in few cases. Histological and immunohistochemical study is compulsory in order to diagnose these tumours which generally shares several features with their gonadal counterparts (1). Concerning the immunohistochemical findings, some authors report different percentages of expression of the antibodies depending on the mediastinal or gonadal localizations (29). The association of these tumours with hematologic malignancies or a Klinefelter syndrome is reported in the literature (28). Besides, these tumours may be associated with somatic-type malignancies which influence their prognosis (1). Because of the rarity of these tumours, no consensual treatment is available. Therapeutic strategies depend on the histological nature, the patient's age, their general health state, the tumour's size and the disease's stage. The therapeutic procedures used are the surgical resection, the radiation therapy and the chemotherapy. In seminomas, the treatment is based upon chemotherapy (28). The necessity of the radiation therapy remains debated (30).

In NST, the cisplatin-based chemotherapy followed by surgical resection has become the standard treatment (15). Lemarié is the only author who proposed a clear therapeutic management for seminomatous and NST (31). The prognosis of the MMGCT is worse than their gonadal counterparts. The cisplatin-based chemotherapy improved dramatically their prognosis. The different histological types influence the prognosis. In fact, the overall 5-year survival of NST is 45% in comparison with 80% for seminomas (15). According to the literature, the overall 2-year survival of our patients with seminoma was 100% and 25% for patients with NST. The histological nature and the clinical staging seem to be the major prognostic factors (32). In our study, the patients with stage I disease survived for a mean period of 3 years (range, 2 to 4 years). Many other factors may be of consideration. They include the association to somatic and hematologic malignancies, the tumour marker level, the complete remission after chemotherapy, the complete resection of the tumour, the recurrences, etc.

CONCLUSION

The primary MMGCT cause generally a diagnostic challenge because of the difficulty of their resection and the little size of the biopsy specimen. Besides, the absence of a primary gonadal localization may be difficult to establish. These tumours have a worse prognosis than their gonadal counterparts. Prognostic factors are multiple and not accurate. The management of these tumours depends on many factors inducing the absence of consensus. A study of the experience of multiple institutes may be helpful in order to establish a unanimous strategy.

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