Disseminated lung cancer or extragonadal germ cell tumour?


ABSTRACT: Two patients are reported in whom an initial diagnosis of disseminated non small cell bronchogenic carcinoma was subsequently changed into a final diagnosis of extragonadal germ cell tumour. The clinical importance of the differential diagnosis between these two malignancies is highlighted and the management of extragonadal germ cell tumours is discussed.


The extragonadal germ cell cancer syndrome was first recognized in 1981 [1]. The syndrome includes all patients with a histopathological diagnosis of poorly differentiated non small cell carcinoma, unknown primary tumour, normal clinical examination of pelvis and testes, and at least three of the following criteria: a) age under 50 yrs; b) large tumour volume in either the midline structures, lymph nodes, or lung; c) rapid tumour progression; and d) high serum β human chorionic gonadotrophin (β-HCG) or α-fetoprotein (AFP) [2].

Retrospective analysis, including pathology review with accessory staining techniques, changes the initial diagnosis of extragonadal germ cell tumour in up to 30% of these patients to a final diagnosis of poorly differentiated adenocarcinoma, undifferentiated carcinoma or sarcoma, lymphoma or melanoma [2].

Thus, some patients with non small cell bronchogenic carcinoma can present with the clinical features of extragonadal germ cell cancer and the reverse is equally true. Since prognosis and therapy for the two disorders differ widely, correct diagnosis is of the utmost importance.

Two illustrative case reports are presented, and true extragonadal germ cell tumours are reviewed.

Case reports

Case 1

A 47 year old man was admitted with a two months' history of productive cough, haemoptysis and dyspnoea. Recently, he developed nonremitting hoarseness and episodic dull pain in the right chest. He suffered severe night sweats, marked asthenia and a 4 kg weight loss. History further revealed a 40 pack yrs' tobacco abuse.

Physical examination was unremarkable. Chest X-ray showed a right-sided paratracheal tumour, enlarged hilus, and infiltrate in the upper lobe. Computerized axial tomography (CAT) scan of the chest disclosed a 10 cm diameter tumour in the middle and posterior mediastinum, hilar lymphadenopathy, and numerous small nodules in the upper lobe. Bronchoscopy was normal. Percutaneous fine needle aspiration of the principal tumour revealed poorly differentiated large cell carcinoma.

Staging examinations demonstrated a 4.5 cm diameter retroperitoneal tumour near the left adrenal gland. Laboratory tests showed elevated serum lactate dehydrogenase (LDH) (260 U·l⁻¹, normal <240 U·l⁻¹). Serum carcinoembryonic antigen (CEA) and (NSE) were normal. A diagnosis of Stage IV non small cell lung cancer was made.

However, the cytopathology of the tumour, its midline distribution and the presence of pulmonary metastases prompted exclusion of a germ cell tumour. Serum HCG was normal. Serum AFP was elevated (5,500 U·ml⁻¹, normal <10 U·ml⁻¹). Clinical examination and ultrasonography of the tests being normal, the retroperitoneal tumour was surgically removed. Histopathology revealed embryonal carcinoma, with immunopathology showing HCG in most and AFP in some tumour cells. A final diagnosis of extragonadal non-seminomatous germ cell tumour Stage IV L2 was made.

The patient received three courses of bleomycin-vincristine-cisplatin (BOP) combination chemotherapy. Partial remission was obtained, and two courses of etoposide-ifosfamide-cisplatin (VIP) combination chemotherapy
Eight months from the last administration of chemotherapy, normal serum HCG and further reduction of the mass supports the idea of a major clinical response with only scar tissue or mature teratoma in the residual tumour mass.

Discussion

Extragonadal germ cell tumours (EGCT) are germ cell tumours (GCT) without clinical or ultrasonographic evidence of a testicular tumour. They represent less than 10% of all GCT [3]. The origin of EGCT is to be found in primordial germ cells, migrating to the midline structures in the fifth or sixth week of embryonic life and failing to incorporate in the primary sex cords [4].

Most EGCT are primarily located in the midline structures such as the retroperitoneum (25%), the mediastinum (25%), or both the retroperitoneum and the mediastinum (>45%) [4]. Metastatic disease most often affects the lung, but liver, bone and central nervous system metastases may occur [4].

The patients, mean age is 25 yrs (range: 10–70 yrs). Apart from rapidly deteriorating general condition and weight loss, the clinical features of EGCT are determined by the location and bulk of the primary tumour and its metastases. They include pain in the chest, abdomen or back, and dyspnoea, cough and haemoptysis [4].

In over 80% of the patients increased serum LDH, HCG and/or AFP levels are noted [4, 5]. HCG values >500 IU·ml⁻¹ (100 ng·ml⁻¹) in the absence of pregnancy and choriocarcinoma, andAFP values >200 U·ml⁻¹ in the absence of hepatocellular carcinoma are pathognomonic for germ cell tumour [6].

Table 1 summarizes the nomenclature, and the tumour markers and immunopathology findings in germ cell tumours. In EGCT, more choriocarcinomas and yolk sac tumours, and fewer seminomas are found than in testicular GCT; embryonal carcinoma is also more prevalent than teratocarcinoma.

Pathological examination of the testes is advocated in patients with a palpable testicular abnormality, a recent change in testicular size or consistency, an abnormal testicular ultrasound, a history of cryptorchidism, and if the primary tumour is choriocarcinoma [7]. However, we feel that orchidectomy in cryptorchid patients should be restricted to the following conditions: a) abdominal testes; b) atrophic testes when either low plasma testosterone level or oligospermia are found; c) previous chemotherapy were added. Increasing serum AFP and LDH levels and expanding tumour mass on chest X-rays prompted the discontinuation of this chemotherapeutic combination. Radiation therapy to the mediastinum and right upper lobe arrested tumour progression and serum AFP again decreased to 40 U·ml⁻¹.

The patient died with progressive disease 16 mths after the initial diagnosis.

Case 2

A 60 yr old man was first seen with an eight months, history of productive cough and dyspnoea. Chest X-ray and bronchoscopy were reported normal six months previously. Recently, he developed haemoptysis. Severe asthenia and a 2 kg weight loss were noted. History revealed a 40 pack yrs' tobacco abuse.

Physical examination was unremarkable. Chest X-rays showed a right hilar mass and bilateral pulmonary nodules. CAT scan of the chest confirmed a 5 cm diameter tumour invading the upper anterior mediastinum, and multiple intrapulmonary nodules, the largest of which measured 3 cm in diameter. Bronchoscopy was normal. Transbronchial biopsy in a right upper lobe nodule revealed poorly differentiated large cell carcinoma. Staging examinations demonstrated an enlarged right adrenal gland. Serum CEA (9.1 ng·ml⁻¹, normal <6 ng·ml⁻¹) was slightly increased. SerumNSE was normal. A diagnosis of Stage IV non small cell bronchogenic carcinoma was made.

The tumour histopathology, its midline distribution, and the presence of pulmonary metastases again prompted exclusion of a germ cell tumour. Serum AFP was normal. The high serum HCG (2,900 mU·ml⁻¹, normal <5 mU·ml⁻¹) level, the positive HCG stain on immunopathology of the transbronchial biopsy material, and the normal clinical examination and ultrasonography of the testes, led to a final diagnosis of extragonadal non-seminomatous germ cell tumour Stage IV L3.

The patient received three courses of BOP and three courses of VIP combination chemotherapy. Re-evaluation revealed a reduction in volume of the largest tumour mass and disappearance of the smaller lung metastases, normal right adrenal gland, and normal serum HCG. Surgical extirpation of the residual mass was refused. Over the ensuing months, the patient's general condition markedly improved.
history of testicular GCT; and d) intersex conditions [8]. This approach allows maximal testicular preservation with minimal compromise of patient cure. Patients with metastatic germ cell tumours can now be cured with intensive combination chemotherapy. Since antineoplastic drugs may not reach cytotoxic levels within the testicular tissue, neoplasia might persist in the testicular sanctuary [9, 10] after adequate treatment of the extragonadal cancer.

The prognosis of seminomatous EGCT is similar to that of testicular seminoma, and is governed by pretreatment serum LDH and/or HCG levels [11, 12]. The prognosis of nonseminomatous EGCT is worse than that of testicular malignant teratoma, and is governed by pretreatment serum LDH, HCG and/or AFP levels, the volume of the midline tumour and pulmonary metastases, and the presence of trophoblastic elements [13, 14]. EGCT exhibits larger tumour volumes and more trophoblastic elements than most testicular GCT.

In seminomatous EGCT, the 5 yr disease free survival of patients receiving cisplatin containing combination chemotherapy (>75%) exceeds that of patients receiving radiation therapy (<60%) [11, 12, 15]. In the absence of signs of progressive disease, residual tumour after chemotherapy completion, measuring less than 3 cm in maximal diameter, very rarely contains viable tumour cells and close observation is in order. Larger residual tumour harbours viable tumour cells in up to 40% [16]. Further treatment consists of radiotherapy (35 Gy tumour dose) for mediastinal tumour and surgery for retroperitoneal tumour. If viable tumour is found at surgery, postoperative radiation therapy or chemotherapy are to follow [12].

In nonseminomatous EGCT, the long-term disease free survival of patients receiving standard cisplatin containing combination chemotherapy averages 30–40% [1, 4, 5, 14, 17]; in nonseminomatous testicular GCT, the 5 yr disease free survival ranges from 60–100% depending on the tumour volume [17]. In the absence of signs of progressive disease, all residual tumour after chemotherapy completion should be managed by surgery. If viable tumour is found at surgery, further chemotherapy is required, although 50% of these patients may be cured by surgery alone [18]. Improvement of the therapeutic efficacy of the standard cisplatin-etoposide-bleomycin (BEP) combination chemotherapy regimen by increasing the cisplatin dose intensity and by the incorporation of additional effective drugs such as vincristine and ifosfamide, is currently investigated in randomized treatment protocols (such as BEP vs BOP/VIP) for poor prognosis nonseminomatous GCT [19].

Since the five year survival of patients with stage IV non small cell bronchogenic carcinoma is well below 10% [20], the differential diagnosis between this disorder and EGCT bears considerable prognostic significance.

Conclusion

In every patient presenting with a poorly differentiated large cell carcinoma of seemingly pulmonary origin, a voluminous mediastinal and/or retroperitoneal tumour mass, and absence of visible tumour at bronchoscopy, an extragonadal germ cell tumour must be included in the differential diagnosis. Serum HCG and AFP must be determined, and clinical examination and ultrasonography of the testes must be performed. Informing the pathologist of the clinical suspicion of a germ cell tumour and obtaining more tissue for examination, if necessary, is often very useful in reaching the correct diagnosis. This is of paramount importance to the patient as the prognosis of disseminated non small cell bronchogenic carcinoma is very poor, whereas extragonadal germ cell tumour may be curable.

References


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