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## **Chemotherapy in the management of disseminated thymoma: a case report and the authors' own experience**

### **Abstract**

Thymomas are tumours originating from the epithelial tissue of the thymus. While surgery is the mainstay of therapy in thymoma, chemotherapy may significantly improve the prognosis. Effective chemotherapy may be administered in the neoadjuvant setting (prior to surgery), in the adjuvant setting (following surgery), may be combined with radiotherapy or be used for palliation in disseminated disease. We report a case of a 66-year-old male with advanced thymoma who received second-line treatment with a good outcome.

**Key words:** thymoma, chemotherapy, complete response

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### **Introduction**

Thymomas are primary mediastinal tumours. Although they are the second most common mediastinal tumours after mediastinal tumours of neural origin, their prevalence is low (0.15 per 100,000 per year) [1]. Thymomas originate from the epithelial tissue of the thymus but may also contain normal lymphatic elements of the gland. The malignant nature of thymoma is determined by the presence of cells of epithelial origin [2]. The aetiology and the risk factors for thymomas are unclear. These tumours are most commonly discovered incidentally and their peak incidence is in the fourth and fifth decades of life. The mean age at diagnosis is 52 years [3].

The management of thymic tumours involves surgery, radiotherapy and chemotherapy.

The significance of these treatment modalities varies depending on the stage of the disease [4]. The role of chemotherapy in the management of thymomas continues to be disputed due to the low incidence of these tumours and the resulting difficulties in conducting clinical trials in large groups of patients. Thymomas are believed to be chemosensitive tumours. Chemotherapy has been used in the neoadjuvant setting and in combination with radiotherapy [5]. Chemotherapeutic agents used in the management of thymoma include cisplatin, doxorubicin, iphosphamide, cyclophosphamide, vincristine, etoposide and bleomycin. Due to their thymolytic and oncolytic effects, glucocorticosteroids also play a role in the management of thymoma. Concomitant administration of octreotide increases their efficacy [6–8].

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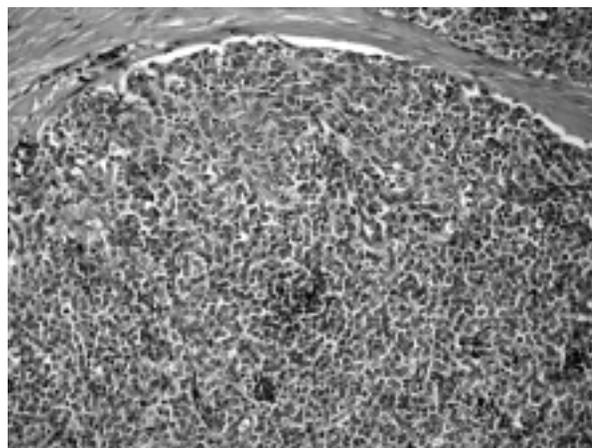
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## Case presentation

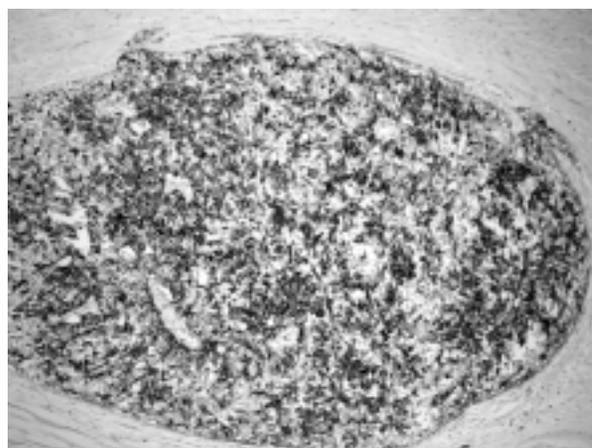
In December 2007 a 66-year-old male with hypertension underwent a chest X-ray and an abdominal and pelvic ultrasound scan. As the X-ray revealed widening of the mediastinum, a chest CT scan was recommended. The chest CT scan revealed an extensive, heterogenous, well-circumscribed, partly solid and partly cystic mass located in the mediastinum and measuring 86 × 53 × 76 mm. The mass extended to the posterior surface of the manubrium sterni and its posterior part was found to be adjacent to the aortic arch, pulmonary trunk and the left pulmonary artery. The patient did not have any tumour-related complaints at that time. The abdominal and pelvic ultrasound was unremarkable. Upon the receipt of the chest CT scan report bronchoscopy was performed. The cytology of the bronchial brushings only revealed morphotic elements of the lower airways. Following consultation by thoracic surgeons the patient was qualified for surgery. On 14 February 2008 the patient underwent left-sided thoracotomy and the mediastinal mass was removed.

Subsequent histopathology established the diagnosis of type B3 thymoma (according to the 1999 World Health Organization [WHO] classification) with neuroendocrine differentiation [9]. The tumour histology revealed well-circumscribed and expanding clusters of cells embedded in a fibrous stroma. The tumour cells of intermediate sizes (2–3 times the red blood cell size) expressed cytokeratins AE1/AE3 and CK5/6. The number of scattered lymphocytes around the epithelial clusters was very low. The tumour cells had round or oval nuclei with granular chromatin and conspicuous nuclei. Chromogranin expression was evident in 20% of the cells partially in a diffuse pattern and partially in the form of a uniform focus. Synaptophysin expression was present only in 2% of the single diffuse cells.

The surgery report read that the partially solid and partially cystic mass infiltrated the surrounding adipose tissue and slightly infiltrated the left pulmonary artery. Following a review of the patient's records it was concluded that the resection had been non-radical (R1) and the stage of the disease was established at III according to the Masaoka classification [10]. The patient was then qualified for adjuvant radiotherapy. From 20 March to 19 May 2008 the patient received photon radiotherapy at 20 MV. The irradiation area included the mediastinum up to the total dose of 50 Gy, followed by irradiation of the tumour bed up to the total dose of 54 Gy/t. The fractional dose

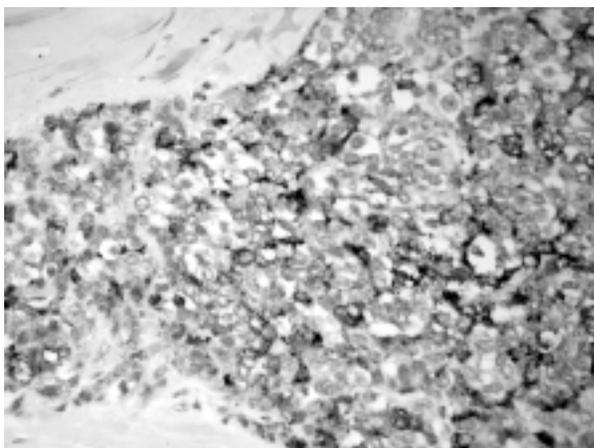


**Figure 1.** Microscopic picture of the thymoma B3 in hematoxylin-eosin stain

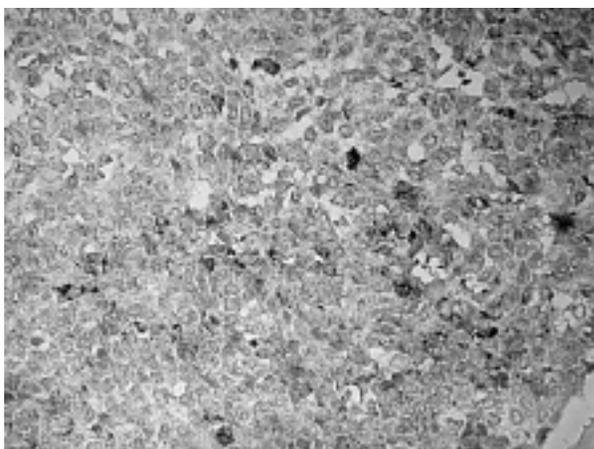


**Figure 2.** Immunohistochemistry expression of cytokeratin AE1/AE3

was 2 Gy. Radiotherapy was complicated by a WHO grade 1 radiation-induced oesophagitis. Two months after completion of radiotherapy a follow-up abdominal CT scan revealed multiple metastatic masses in the liver. Following a consultation at the Clinical Oncology Department of the Oncology Institute in Gliwice, Poland, given the patient's good general condition, no co-morbidities and normal liver function tests, a decision was made to initiate systemic chemotherapy according to the ADOC regimen (anthracycline, cisplatin, cyclophosphamide and vincristine) at standard doses and in the recommended 21-day cycles. From 23 July to 30 December 2008 the patient received six cycles of systemic treatment. Based on the imaging studies evaluating treatment response (abdominal and pelvic ultrasound and CT scans) a complete regression of the liver metastases was determined. A solitary cyst in segment 6 of the liver was the only finding. The systemic treatment was tolera-



**Figure 3.** Immunohistochemistry expression of chromogranin



**Figure 4.** Immunohistochemistry expression of synaptophysin

ted very well and the patient did not report any additional complaints. No haematologic toxicities were observed during treatment. Upon the completion of systemic chemotherapy the patient was qualified for  $^{68}\text{Ga}$  DOTATATE PET, which revealed no pathological tracer accumulation. The patient then remained under ongoing care of the Chemotherapy Outpatient Service and underwent follow-ups at the Department of Nuclear Medicine.

In August 2009, a follow-up abdominal CT scan revealed a relapse in the form of isolated liver metastases. Given the time that had elapsed since the completion of first-line treatment (8 months) the patient was re-evaluated and qualified for second-line treatment chemotherapy based on cisplatin and etoposide. During qualification for the treatment the patient did not report any additional complaints but had been under a cardiologist's care due to periodic arrhythmias and periodic angular symptoms. He was taking antiarrhythmics, nitrates, an ACE inhibitor and inotropes. The pa-

tient commenced chemotherapy on 1 October 2009. After receiving the first cycle the patient developed moderate hypersensitivity to cisplatin manifested by dyspnoea and generalised urticaria, which resolved upon symptomatic treatment. Chemotherapy infusions were continued and the patient received prolonged premedication with glucocorticosteroids. By January 2010 the patient had received four cycles of PE chemotherapy. The tolerability of the two agents was worse than that of first-line treatment: serum creatinine and urea were gradually increasing and signs of incipient renal failure appeared. The patient complained of increasing fatigue and asthenia and severe periodic dyspnoea. Evaluation of treatment response after the fourth cycle revealed a partial regression of liver metastases. However, despite the good response to systemic treatment chemotherapy was discontinued due to the worsening of the patient's clinical condition.

After discontinuation of cancer treatment the patient was transferred under the care of his local physician and saw his chemotherapy specialist for follow-up visits. After discontinuation of systemic therapy the patient's condition improved: the dyspnoea resolved and the signs of renal failure did not worsen. Eight months (in September 2010) after completion of the second-line chemotherapy imaging studies revealed progression of the disease in the form of relapse in the lungs and a further qualitative and quantitative progression of the liver metastases. Laboratory tests revealed anaemia, thrombocytopenia and elevated liver function tests. The patient continued to deteriorate. He remained under the care of a hospice team at his home. His treatment regimen at that time included high-dose glucocorticosteroids (Dexaven 32 mg/day). The patient passed away in November 2010 and the direct cause of death was cardiovascular insufficiency — pulmonary oedema, and left-sided hemiparesis. The patient had survived 33 months after the diagnosis.

## Discussion

Survival rates of patients with advanced thymoma following complete resection of the primary tumour continue to be unsatisfactory. According to the literature data, 5-year survival rates are 85–95% for stage I and only 50–60% for stage IV disease, while 10-year survival rate range from 35% to 50% [11]. Disseminated disease is observed in about 30% of stage III patients and in nearly all stage IV patients [12]. Metastatic thymoma is reported in about 5% of the cases with the pleura, pericar-

dium, liver, bone and the central nervous system being the most common sites [13, 14].

Neuroendocrine (NE) differentiation may take the pure form, the form of a neuroendocrine tumour or the form of scattered neuroendocrine cells in other non-neuroendocrine tumours. Neuroendocrine differentiation is considered one of the many directions of differentiation that occur in malignant tumours [15]. The ability of thymic epithelial cells to produce various hormones and neuropeptides which are primarily found in the pituitary gland has been confirmed [16]. Using electron microscopy, Wick et al. identified cytoplasmic neurosecretory granules in high-grade and spindle-cell carcinomas of the thymus [17]. Expression of neuroendocrine markers has been described by Libero et al. in thymic carcinomas and its absence in thymomas. The authors emphasise that the presence of neuroendocrine differentiation may be a marker of malignant nature [18]. According to Japanese authors (Hishima et al.), scattered neuroendocrine differentiation is associated with epithelial expression of CD5 and the absence of immature lymphocytes in thymic carcinomas and atypical thymoma (WHO type C and B3 tumours, respectively) [19].

Thymomas are classified as tumours sensitive to selected cytostatic agents, although the role of chemotherapy in the treatment of these tumours is still being researched and debated. Chemotherapy leads to considerably high objective response rates and to improved disease-free survival and survival rates [20]. Systemic treatment may also lead to satisfactory response, both clinical and radiological. Regression of nodal involvement and the resolution of fever, of superior vena cava symptoms and of vocal cord paralysis are observed. Chemotherapy improves paraneoplastic symptoms accompanying thymomas, such as myasthenia gravis (30–45%), pure red-cell aplasia and hypogammaglobulinaemia (2–5%) [11, 12]. The cytotoxic agents decrease the tumour mass leading to an improvement of chest discomfort and pain, dyspnoea and dry cough. Response to chemotherapy is believed to occur in 50–70% of the patients [11]. The principal chemotherapy regimens used in the systemic treatment of thymomas are multi-drug regimens, such as ADOC (doxorubicin, cisplatin, vincristine, cyclophosphamide), PAC (cisplatin, doxorubicin, cyclophosphamide), PE (cisplatin, etoposide) and VIP (vincristine, iphosphamide, cisplatin). The available publications emphasise that treatment with multi-drug regimens results in higher response rates of 50–90% and more durable responses [22, 23]. According to Moor and Hejna, on the other hand, re-induction treatment

in patients with the diagnosis of thymoma may be considered in cases of remission of at least 6 months' duration following first-line treatment [5, 24]. Radiotherapy also plays a role in Masaoka stage II to IVA thymomas [10]. In stage II disease, radiotherapy is offered to patients following non-radical surgery. According to the available literature, adjuvant radiotherapy reduces the rate of local recurrences from 28% to 5% [25–27]. There are, however, studies that show little benefit of adjuvant radiotherapy [28].

The case presented in this paper supports the efficacy of chemotherapy and justifiability of using this modality in patients with advanced disease in the form of metastases in parenchymal organs. The response benefit of second-line treatment has also been confirmed. Due to the cardiovascular co-morbidities and the cumulative dose of anthracyclines the recommended re-induction was not offered despite sufficient time between the completion of first-line chemotherapy and recurrence of the tumour.

The outcomes of treatment and the survival (2 years and 9 months) we observed may also be associated with the adjuvant radiotherapy used. Due to the lack of unequivocal diagnosis of thymoma before the surgery the patient failed to receive the recommended neoadjuvant chemotherapy, which — according to the available literature — leads to treatment responses in at least half of the patients with rates ranging from 40% to 90% [5]. One of the factors that contributed to the prolonged survival was undoubtedly the use of high-dose glucocorticosteroids, which have oncolytic effects.

Despite the reported chemosensitivity of thymomas the outcomes of systemic treatment continue to be unsatisfactory. Some reports describe epidermal growth factor receptor (EGFR) immunoreactivity, and overexpression is associated with aggressive forms of thymic tumours [29, 30]. Further studies are therefore necessary and should focus on the search for molecular markers allowing to accurately identify prognostic factors for this tumour.

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