Case Report

Yolk sac tumour in the anterior mediastinum

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SUMMARY. The case is presented of a patient who was hospitalized for the investigation of an anterior mediastinal mass, which proved to be a yolk sac tumour. The patient was a 33 year-old male non smoker who presented at the emergency respiratory department with a one month history of persistent dry cough with no relevant past medical history. Clinical examination revealed non specific chest sounds, restriction on spirometric testing, anaemia, an abnormal blood of albumin/globulin ratio and a high serum level of LDH. Chest X-ray and computed tomography (CT) showed marked widening of the anterior mediastinum with a lobed edge to the right cardiac margin, right sided pleural effusion and nodular opacities in the left upper and lower lung fields. The blood level of beta human chorionic gonadotropin (β-HCG) was zero, while the level of alpha 1 fetoprotein (AFP) was extremely high. The histological examination revealed a germ cell neoplasm with the characteristics of a yolk sac tumour. *Pneumon 2013, 26(4):361-365.*

CASE REPORT

A 33 year-old male non smoker attended the emergency respiratory department complaining of a persistent dry cough for one month. He had not previously consulted a doctor and had no other symptoms. The chest X-ray showed sizable widening of the anterior mediastinum, coin lesions in the left upper and lower lung fields and right sided pleural effusion (Figure 1). Diagnostic thoracentesis was performed, which produced a polymorphonuclear exudate with 7,000 cells/μl (neutrophils: 45%, lymphocytes: 40%, monocytes: 15%). Further tests of the pleural fluid showed: Hct: 1.4%, glucose: 63 mg/dl, total protein: 5.20 g/dL, LDH: 5,740 IU/L, pH: 7.39, and the fluid sample was sent for cytology. Blood testing revealed: Hb: 10.2 gr/dL, Hct: 32.2%, LDH: 1,271 IU/L, albumin: 3.3 g/dL, globulin: 4.2 g/dL.

Computed tomography (CT) of the chest showed a sizeable mass occupying the anterior mediastinum, nodular lesions in the left lung (two in the left upper lobe and a larger lesion in the left lower lobe) and a pleural effusion on the right side, as already seen on the chest X-ray. The CT showed, in addition, pericardial effusion and evidence of pressure on the superior vena cava with narrowing but no infiltration from the central mass (Figures

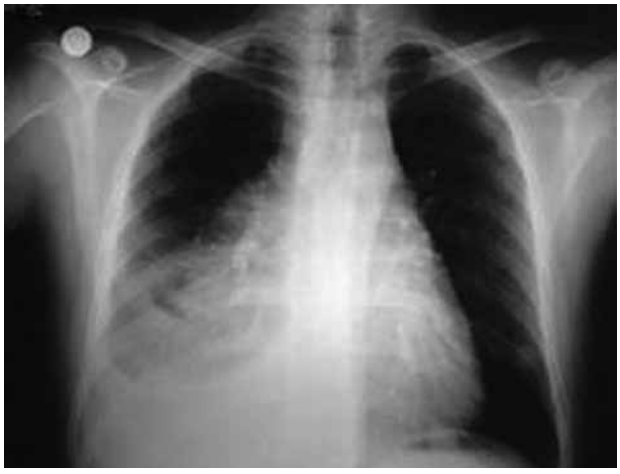

FIGURE 1. Chest X-ray of 33 year-old male with a one month history of dry cough.

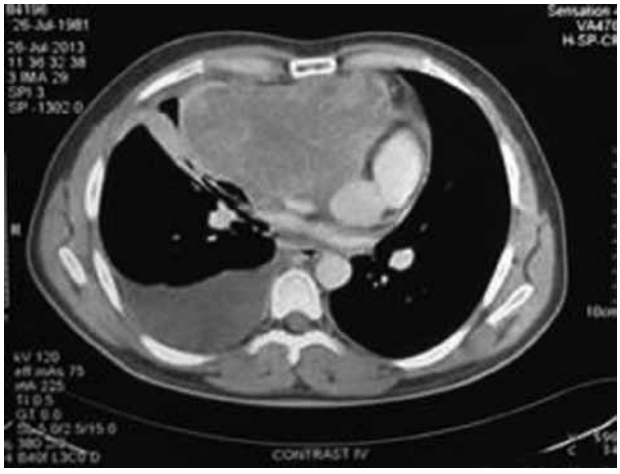

FIGURE 2. Chest computed tomography of 33 year-old male with a one month history of dry cough.

2, 3). Meticulous clinical examination revealed no signs of the superior vena cava syndrome (i.e., swelling of the eyelids, head-and neck swelling, jugular distension, venous markings).

The initial differential diagnosis included lymphoma (because of the patient's age, the location of the mass, anaemia and inversion of the serum albumin/globulin ratio), extragonadal germ cell tumour (EGCT) and thymoma. However, the first hypothesis was soon rejected as no mediastinal lymph nodes were identified. To investigate the diagnosis of EGCT a series of examinations were conducted, including testicular ultrasound and CT of the brain and upper and lower abdomen, which were all normal.

The blood levels of beta human chorionic gonadotrophin (β-HCG) was zero, but the blood level of alpha 1 fetoprotein (AFP) was extremely high, >500mg/L (normal range <15mg/L). These findings supported the tentative diagnosis of a non-seminomatous germ cell tumour. In order to verify the diagnosis, fine needle aspiration, the least invasive method, was preferred.

At the time of the biopsy, three samples of pleural fluid had already been sent for cytological examination, which were all negative for malignancy. The histopathological report from the mediastinal tissue biopsy revealed neoplasm of the germ cells with elements indicating a yolk sac tumour but without excluding the possibility of gross tumour. Immunohistochemical testing of the neoplastic cells showed positivity for Ck 8/18, AE1/AE3, AFP (focal), TTF-1 (partially faded) and negativity for Ck 7, EMA, CD 56, CD 45, confirming the diagnosis of yolk sac tumour.

With this diagnosis, a triple combination chemo-

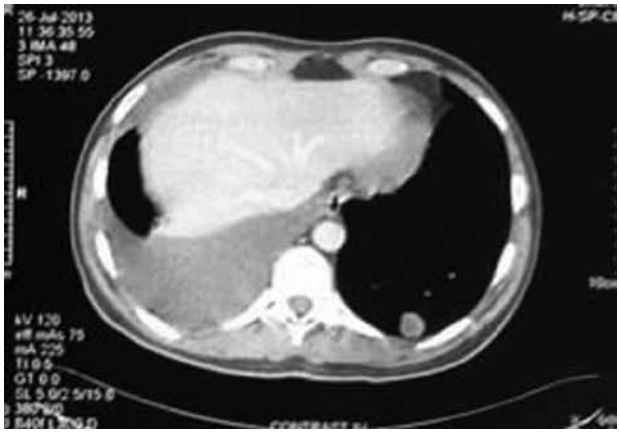

FIGURE 3. Chest computed tomography of 33 year-old male with a one month history of dry cough.

therapy scheme was prescribed, consisting of Bleomycin-Etoposide-Cisplatin (BEP). The possibility of future surgical resection would depend on the positive response to chemotherapy after the first four cycles and restaging of the disease.

DISCUSSION

The most common diseases which may present as a mediastinal mass are thymomas, neurogenic tumours and benign cysts, with a cumulative rate of approximately 60%.[1] Bronchogenic cysts, germ cell tumours and neurogenic tumours represent 80% of the mediastinal masses presenting during childhood, while primary neoplasms

of the thymus, thyroid masses and lymphomas are the most common in adults.[1]

The mediastinum can be described in many anatomical ways. Most clinicians simply divide it into anterior, middle and posterior mediastinum, based on the lateral chest X-ray.[2,3] Mediastinal masses are detected in the anterior mediastinum in 50% of cases.[4]

Regarding the anterior mediastinum, masses with a wide variety of dimensions could be attributed to: thymomas (thymic carcinoma, carcinoid of the thymus, thymolipoma, cysts of thymus, thymus hyperplasia), lymphomas (Hodgkin, non-Hodgkin), germ cell tumours (seminoma, non seminomatous germ cell tumour and teratoma), goitre, parathyroid adenoma, pericardial cysts, and more rarely: lipoma, liposarcoma, angiosarcoma, mediastinal lymphangioma.[3]

Mediastinal masses are usually discovered incidentally. At least half of the patients with a mediastinal mass are asymptomatic and their disease is detected on chest X-ray performed for another reason. Approximately 80% of asymptomatic masses are benign, while more than half of the masses that present with symptoms are malignant.[5-7] The symptoms are due to the external pressure from the mass or its infiltration into adjacent intrathoracic structures.[5,6]

The precise incidence of primary mediastinal masses is difficult to calculate accurately, but it has been estimated at approximately 1/100,000 population / year. Mediastinal tumours in almost 10-15% of adults and 25% of children originate from germ cells[6,8,9], of which 3% develop in the posterior mediastinum.[10] Tumours arising from the germ cells are categorized into teratomas, teratocarcinomas, seminomas and non-seminomatous carcinomas, including choriocarcinoma, embryonal carcinoma, yolk sac carcinoma and mixed type carcinoma. It has been argued that these masses originate from residual germ cells which did not migrate during embryogenesis, remaining in the mediastinum.[11,12]

Yolk sac tumours appear in both men and women and are usually associated with the testes and ovaries. When the testes and ovaries are not the primary site, the tumours are called extragonadal yolk sac tumours and these are usually located in the mediastinum.[13] Other reported sites of yolk sac tumours are the pineal gland, head, neck, lung, stomach, liver, omentum, retroperitoneal space, prostate, intrarenal even the vagina or the pudenda.[13-17] The yolk sac tumour constitutes about 40-50% of non-seminomatous tumours from germ cells in the testes of adults.[18,19] The pathogenesis is generally unknown, but it has been speculated that hypermethylation of the promoter of the RUNX3 gene and overexpression of GATA-4, a transcription factor that regulates the differentiation and function of the endoderm of the yolk sac, may play an important role.[20,21]

Yolk sac tumours give positive staining on immunohistochemical testing for AFP[22], and secrete substances such as AFP, β-HCG and cytokeratin (CEA) which can be detected in the serum and may even contribute to clinical symptomatology, (e.g., gynaecomastia) in 50% of cases.[6,22]

AFP is considerably increased in yolk sac tumour, while the β-HCG is raised in choriocarcinoma and absent in yolk sac tumour. AFP is not a specific serum test for yolk sac tumour, however, as it is also detected in other conditions, including hepatocellular carcinoma and hepatoblastoma.[23] Other diagnostic markers are glypican-3 and SALL4.[14,24] The yolk sac tumour, as all the non-seminomatous germ cell tumours, is associated with Klinefelter's syndrome (up to 20% of patients suffer from the syndrome)[25], a genetic disorder in which there is at least one extra X chromosome on the standard human male karyotype (i.e., XXY instead of XY) and also with haematological malignancies such as acute leukaemia and myelodysplastic syndrome.[26]

The treatment of yolk sac tumours is similar to that of other non-seminomatous germ cell tumours. Significant results have been documented from chemotherapeutic schemes based on cisplatin, with 50% of patients achieving long-term survival.[11,26-28] A widely accepted chemotherapy scheme is Bleomycin-Etoposide-Cisplatin (BEP), which requires at least 4 cycles.[27,29] The survival rate is higher for patients who show a decrease in the serum level of AFP after chemotherapy, and in cases with resectable tumors.[30,31] Surgical resection is recommended particularly when factors such as AFP remain high after 4 cycles of chemotherapy.[32] Even extremely large tumours in this category may respond to aggressive chemotherapy.[33] Rescue treatment includes bone marrow transplantation when necessary.[34,35]

Concerning prognosis, five year survival is achieved in about 65% of cases following appropriate treatment.[36] The average age at diagnosis is 18 years for yolk sac tumour, while it rarely appears after the age of 30 years.[37] Regarding EGCT, Afro-Americans have the worst prognosis[36] and Chinese have poorer prognosis than the inhabitants of Western countries.[38] One study showed that only 7% of Indians with EGCT achieved long-term survival after chemotherapy[39], and it is clear that the role of race and ethnicity justifies further investigation. It has also been documented that EGCT in the mediastinum has a worse

prognosis compared to other sites.[38-40] Regarding novel therapeutic approaches, new techniques have been proposed which include the use of humanized antibodies against the receptor surface molecules of cancer cells, inhibitors of serine-threonine, tyrosine kinase inhibitors and others.[41]

REFERENCES

1. Laurent F, Latrabe V, Lecesne R, et al. Mediastinal masses: diagnostic approach. Eur Radiol 1998;8:1148–1159.
2. Whiteen CR, Khan S, Munneke GJ, et al. A diagnostic approach to mediastinal abnormalities. Radiographics 2007;27:657–671.
3. Fraser R, Paré J, Fraser R, et al. The normal chest. In: Fraser R, Paré J, ed. Synopsis of Diseases of the Chest, 2nd ed. Philadelphia: WB Saunders; 1994:1-116.
4. Tomiyama N, Honda O, Tsubamoto M, et al. Anterior mediastinal tumors: diagnostic accuracy of CT and MRI. Eur J Radiol 2009;69:280–288.
5. Silverman NA, Sabiston Jr DC. Mediastinal masses. Surg Clin North Am 1980;60:757-777.
6. LeRoux BT, Kallichurum S, Shama DM. Mediastinal cysts and tumors. Curr Probl Surg 1984;21:1-76.
7. Cohen AJ, Thompson L, Edwards FH, et al. Primary cysts and tumors of the mediastinum. Ann Thorac Surg 1991;51:378-384.
8. Takahashi K, Al-Janabi NJ. Computed tomography and magnetic resonance imaging of mediastinal tumors. J Magn Reson Imaging 2010;32:1325–1339.
9. Dehner LP. Germ cell tumors of the mediastinum. Semin Diagn Pathol 1990;7:266-284.
10. Duwe BV, Sterman D, Musaniet A. Tumors of the mediastinum. Chest 2005;128:2893–2909.
11. Nichols CR. Mediastinal germ cell tumors. Semin Thorac Cardiovasc Surg 1992;4:45-50.
12. Albers P, DüsseldorfIn. 10th edition of the European Association of Urology Guidelines. Parsons KF, editor. The European Association of Urology; 2010.
13. Toner GC, Geller NL, Lin SY, Bosl GJ. Extragonadal and poor risk nonseminomatous germ cell tumors. Survival and prognostic features. Cancer 1991;67:2049–2057.
14. Mei K, Liu A, Allan RW, et al. Diagnostic utility of SALL4 in primary germ cell tumors of the central nervous system: a study of 77 cases. Mod Pathol 2009;22:1628–1636.
15. Saxman SB, Nichols CR, Einhorn LH. Salvage chemotherapy in patients with extragonadal nonseminomatous germ cell tumors: the Indiana University experience. J Clin Oncol 1994;12:1390–1393.
16. Cao D, Liu A, Wang F, et al. RNA-binding protein LIN28 is a marker for primary extragonadal germ cell tumors: an immunohistochemical study of 131 cases. Mod Pathol 2011;24:288–296.
17. Gupta R, Mathur SR, Arora VK, Sharma SG. Cytologic features of extragonadal germ cell tumors: a study of 88 cases with aspiration cytology. Cancer 2008;114:504–511.
18. Young RH, Scully RE. Testicular Tumors. Chicago, III: ASCP Press; 1990:38-40.
19. Talerman A. Endodermal sinus (yolk sac) tumor elements in testicular germ-cell tumors in adults: comparison of prospective and retrospective studies. Cancer 1980;46:1213-1217.
20. Kato N, Tamura G, Fukase M, Shibuya H, Motoyama T. Hypermethylation of the RUNX3 gene promoter in testicular yolk sac tumor of infants. Am J Pathol 2003;163:387-391.
21. Siltanen S, Anttonen M, Heikkila P, et al. Transcription factor GATA-4 is expressed in pediatric yolk sac tumors. Am J Pathol 1999;155:1823-1829.
22. Grigor KM, Detre SI, Kohn J, Neville AM. Serum alpha1-foetoprotein levels in 153 male patients with germ cell tumours. Br J Cancer 1977;35:52-58.
23. Eglen DE, Ulbright TM. The differential diagnosis of yolk sac tumor and seminoma. Usefulness of cytokeratin, alpha-fetoprotein, and alpha-1-antitrypsin immunoperoxidase reactions. Am J Clin Pathol 1987;88:328-332.
24. Talerman A. In: Blaustein's Pathology of the Female Genital Tract. 5. Kurman RJ, editor. New York: Springer-Verlag; 2002. Germ cell tumors of the ovary; pp. 967–1033.
25. Nichols CR, Heerema NA, Palmer C, et al. Klinefelter's syndrome associated with mediastinal germ cell neoplasms. J Clin Oncol 1987;5:1290-1294.
26. Nichols CR, Roth BJ, Heerema N, et al. Hematologic neoplasia associated with primary mediastinal germ-cell tumors. N Engl J Med 1990;322:1425-1429.
27. Giannis M, Aristotelis B, Vassiliki K, et al. Cisplatin-based chemotherapy for advanced seminoma: report of 52 cases treated in two institutions. J Cancer Res Clin Oncol 2009 ;135:1495-1500.
28. Heinzelbecker J, Katzmarzik M, Weiss C, Trojan L, Haecker A. During twenty years of Cisplatin-based therapy the face of nonseminomatous testicular germ cell tumors is still changing: an evaluation of presentation, management, predictive factors and survival. Int Braz J Urol 2013;39:10-21.
29. Fizazi K, Culine S, Droz JP, et al. Primary mediastinal nonseminomatous germ cell tumors: results of modern therapy including cisplatin-based chemotherapy. J Clin Oncol 1998;16:725-732.
30. Kang C, Kim Y, Jheon S, et al. Surgical treatment of malignant mediastinal nonseminomatous germ cell tumor. Ann Thorac Surg 2008;85:379-384.
31. Jyothirmayi R, Ramadas K, Jacob R, Gangadharan VP, Nair MK. Primary malignant germ cell tumours of the mediastinum--results of multimodality treatment. Acta Oncol 1997;36:317-321.
32. De Latour B, Fadel E, Mercier O, et al. Surgical outcomes in patients with primary mediastinal non-seminomatous germ cell tumours and elevated post-chemotherapy serum tumour markers. Eur J Cardiothorac Surg 2012;42:66-71.
33. Nichols CR, Catalano PJ, Crawford ED, et al. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B study. J Clin Oncol 1998;16:1287-1293.
34. Nichols CR, Andersen J, Lazarus HM, et al. High-dose carboplatin and etoposide with autologous bone marrow transplantation in

refractory germ cell cancer: An Eastern Cooperative Oncology Group protocol. J Clin Oncol 1992;10:558-563.
35. Nichols CR, Saxman S. Primary salvage treatment of recurrent germ cell tumors: Experience at Indiana University. Semin Oncol 1998;25:210-214.
36. Shah JP, Kumar S, Bryant CS, et al. A population-based analysis of 788 of yolk sac tumors: a comparison of males and females. Int J Cancer 2008;123:2671–2675.
37. Robova H, Rob L, Hrehorcak M, Zoban P, Prusa R. Endodermal sinus tumor diagnosed in pregnancy: a case report. Int J Gynecol Cancer 2007;17:914–933.
38. Hse Y-J, Pai L, Chen YC, Ho CL, Kao WY, Chao TY. Extragonadal germ cell tumor in Taiwan: an analysis of treatment results of 59 patients. Cancer 2002;95:766–774.
39. Bokemeyer C, Hartmann JT, Fossa SD, et al. Extragonadal germ cell tumors: relation to testicular neoplasia and management options. APMIS 2003;111:49–59.
40. Rosti G, De Giorgi U, Wandt H, et al. Solid Tumours Working Party. First-line high-dose chemotherapy for patients with poor prognosis extragonadal germ cell tumors: the experience of the European Bone Marrow Transplantation (EBMT) Solid Tumors Working Party. Bone Marrow Transplant 2004;34:1033–1037.
41. Chieffi P, Chieffi S, Franco R, Sinisi AA. Recent advances in the biology of germ cell tumors: implications for the diagnosis and treatment. J Endocrinol Invest 2012;35:1015-1020.