

[CASE REPORT]

Pleomorphic Carcinoma with Exophthalmos and a Subsequent Diagnosis of Paraneoplastic Syndrome

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Abstract:

The patient was a 75-year-old man who developed polyopia and exophthalmos. Chest computed tomography (CT) revealed a mass in the left upper lobe. A CT-guided biopsy suggested lung adenocarcinoma. He was treated by neoadjuvant chemotherapy followed by left upper lobectomy. He was diagnosed with stage IIB pleomorphic carcinoma postoperatively. Preoperative head magnetic resonance imaging revealed exophthalmos and bilateral swelling of the extraocular muscles. The thyroid function of the patient was within the normal range, and he tested negative for autoantibodies. As his symptoms and swelling of the extraocular muscles improved postoperatively, he was diagnosed with paraneoplastic syndrome.

Key words: exophthalmos, lung cancer, paraneoplastic syndrome

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Introduction

Thyroid eye disease is the most common cause of exophthalmos. Exophthalmos can also be caused by inflammation of intraorbital structures (e.g., orbital cellulitis and myositis), the presence of tumors (e.g., orbital tumors and metastatic tumors in the orbit), morbid obesity, and Cushing's syndrome. Although the incidence rate is unknown, exophthalmos rarely manifests in paraneoplastic syndrome (1, 2).

We herein report a patient with pleomorphic carcinoma who developed exophthalmos as a manifestation of paraneoplastic syndrome.

Case Report

The patient was a 75-year-old man with no medical history. He had visited an optometrist four months prior to visiting our hospital for polyopia. Due to convergent strabismus and increased intraocular pressure, he was prescribed eye

drops and eyeglasses with corrective lenses. He visited his local clinic two months prior to visiting our hospital and underwent chest imaging, which revealed an abnormal shadow, and he was subsequently referred to a hospital.

Chest computed tomography (CT) demonstrated a 50-mm mass in the left upper lobe, leading to a transbronchial biopsy. However, the results were insufficient to make a definitive diagnosis. He was thus referred to our hospital to be assessed for a surgical biopsy and surgery. The findings on physical imaging included moderate exophthalmos (approximately 20 mm for both sides), bilateral lateral gaze palsy, Von Graefe's sign, and Dalrymple's sign. Symptoms related to thyrotoxicosis were not observed.

Blood testing revealed a moderate increase in C-reactive protein (CRP, 2.54 mg/dL) and moderate decrease in hemoglobin (Hb, 11.5 g/dL). There were no other abnormal findings on blood testing, and test results for tumor markers were negative. The patient had normal levels of free-T4, thyroid-stimulating hormone (TSH), and thyroglobulin, which were measured to enable the differential diagnosis of exophthalmos. Furthermore, he tested negative for anti-TSH

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receptor antibody, anti-thyroglobulin antibody, and anti-thyroid peroxidase (TPO) antibody.

Chest X-ray revealed a mass in the left upper lobe (Fig. 1), and a well-defined mass measuring approximately 60 mm in the apex of the left lung and a 10-mm swollen lymph node in the hilum of the left lung were observed on chest CT (Fig. 2). Positron emission tomography (PET)-CT further revealed the accumulation of fluorodeoxyglucose (FDG) in the mass (maximum standardized uptake value: 27.5) (Fig. 3).

A CT-guided biopsy of the mass in the apex of the left lung suggested it to be poorly differentiated lung adenocarcinoma (cT3N0M0, Stage IIB). Based on these findings, the patient was diagnosed with a resectable Pancoast tumor with chest wall invasion (cT3N0M0, Stage IIB) and underwent surgery following induction chemoradiotherapy. Induction chemoradiotherapy consisted of carboplatin and paclitaxel, followed by the administration of a total of 45 Gy to the chest. Following chemoradiotherapy, the maximum diameter of the tumor measured on chest CT decreased from 80 mm to 64 mm. Thus, the patient subsequently underwent upper

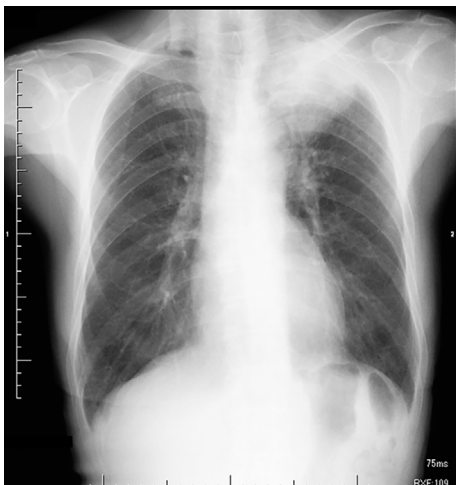


Figure 1. Chest X-ray at the time of admission. The image shows a mass in the left upper lobe.

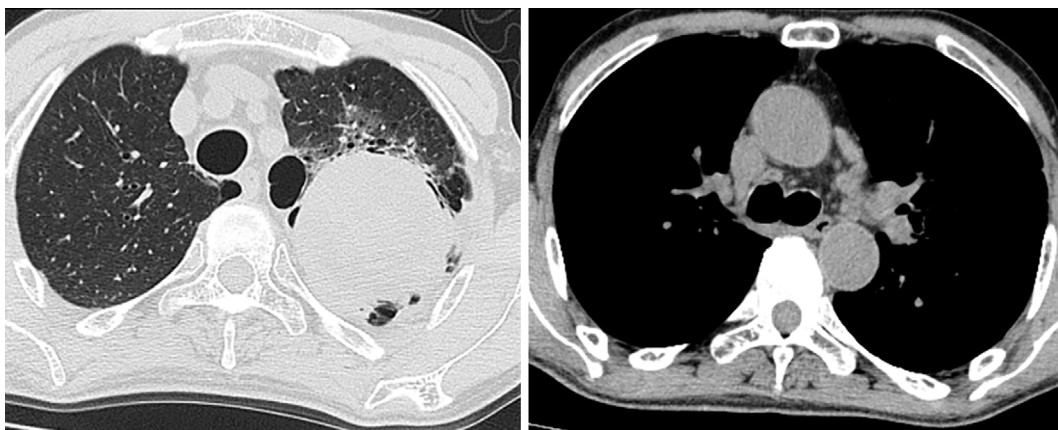


Figure 2. Chest CT at the time of admission. The image shows a well-defined 64×63-mm mass in the apex of the left lung and swelling of the lymph node in the hilum of the left lung.

left lobectomy with parietal pleurectomy, S6 segmentectomy, and mediastinal lymph node dissection.

Regarding the pathology (Fig. 4), the tumor was composed of necrotic tissues and granulation tissues, with infiltration of inflammatory cells. On high magnification of hematoxylin-eosin staining, invasive growth of poorly differentiated pleomorphic carcinoma with giant cells was noted. Immunostaining confirmed the spindle cells and giant cells to be positive for pankeratin and CK7. Collectively, these findings suggested that the tumor in the apex of the lung was pleomorphic carcinoma. The tumor was subsequently diagnosed as pT3N0M0 stage IIB pleomorphic carcinoma, and two-course adjuvant chemotherapy (carboplatin+paclitaxel) was administered.

Preoperative magnetic resonance imaging (MRI) of the orbit demonstrated bilateral exophthalmos and swelling of the extraocular muscles. Thyroid eye disease was suspected based on these findings, and systemic steroid therapy was planned after treatment of the tumor in the apex of the lung. However, the intraocular pressure and vision in both eyes improved by day 8 after surgery, and the patient reported improvements in polyopia by day 10. Bilateral exophthalmos resolved by two months after the surgery, and orbit MRI performed seven months after the surgery revealed improvements in bilateral exophthalmos and swelling of the extraocular muscles (Fig. 5, Table 1, 2). The improvements in both polyopia and exophthalmos soon after surgery suggested that these symptoms had been manifestations of paraneoplastic syndrome caused by pleomorphic carcinoma.

Currently, at four years after the surgery, the patient is well without recurrence of lung cancer or exophthalmos.

Discussion

Reports of exophthalmos as a paraneoplastic syndrome are rare, and to our knowledge, only six cases have been reported to date (Table 3) (1-5).

Among these, five were in men, and one was in a woman. The underlying pathologies were lung cancer (n=4), breast

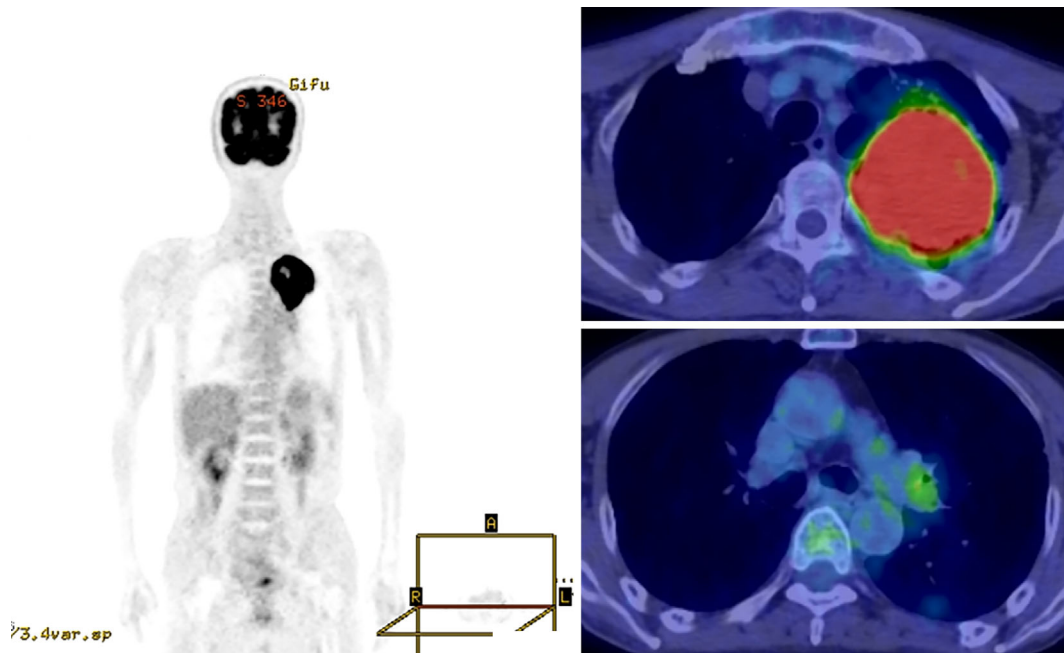


Figure 3. PET-CT image. FDG accumulation is observed in the mass in the apex of the left lung.

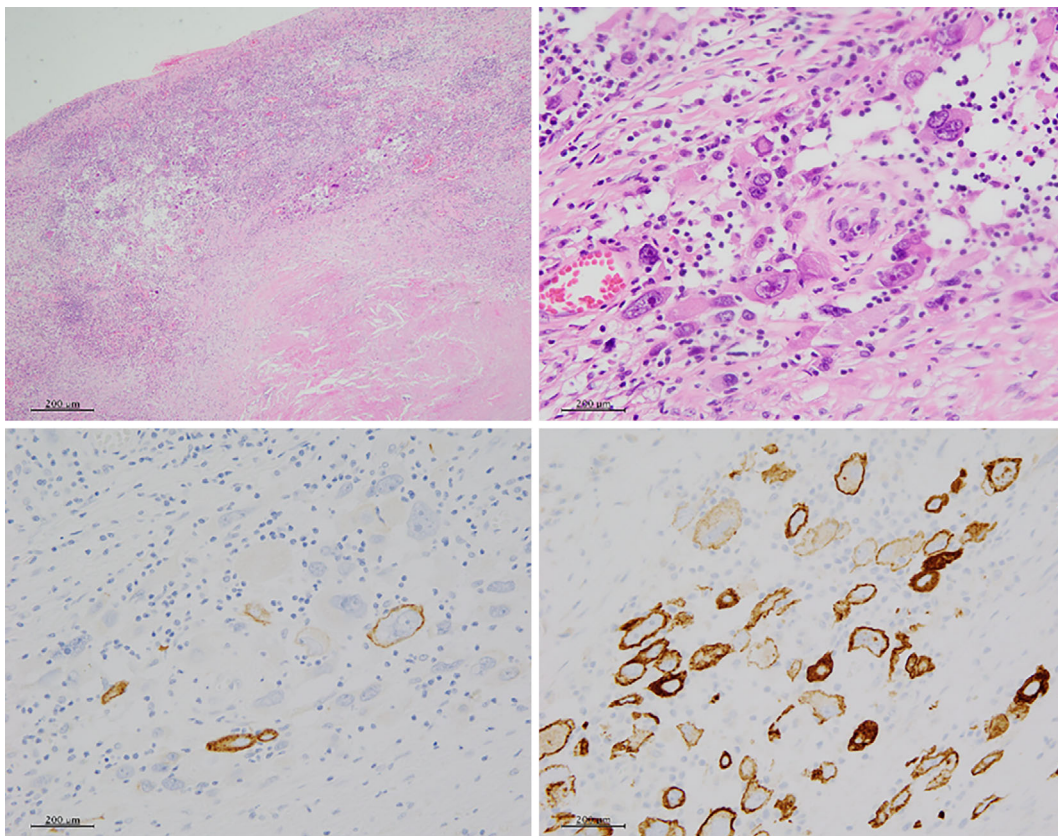


Figure 4. Histopathological findings. Most areas of the tumor consisted of necrotic and granulation tissue, with infiltration of inflammatory cells [left upper, Hematoxylin and Eosin (H&E) staining $\times 40$]. On high-magnification H&E staining, invasive growth of poorly differentiated pleomorphic carcinoma with giant cells was observed (right upper, H&E staining $\times 400$). Immunostaining further demonstrated that spindle cells and giant cells were positive for pankeratin (left lower, pan-cytokeratin staining $\times 400$) and CK7 (right lower, CK7 staining $\times 400$). Based on these findings, the patient was diagnosed with pleomorphic carcinoma.

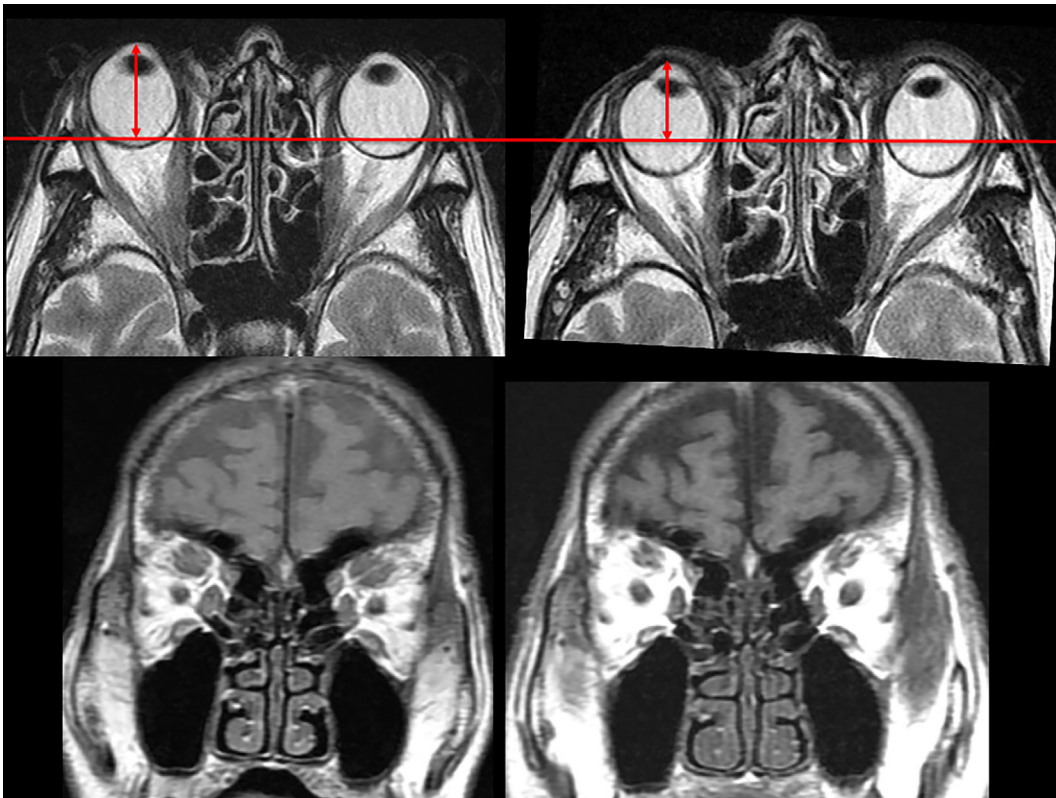


Figure 5. Orbit MRI. The preoperative image (left upper) shows moderate exophthalmos with both eyes located 18 mm away from the line connecting the two orbital rims. Orbit MRI performed 7 months after surgery (right upper) shows improvements in exophthalmos, with both eyes located 14 mm away from the orbital rims (red line). Preoperative swelling was primarily in the superior, inferior, and medial rectus muscles (left lower). Following surgery, swelling of the superior rectus muscle improved (right lower).

Table 1. Degree of Exophthalmos.

Degree of exophthalmos (mm)	Preoperative	Postoperative	Postoperative - Preoperative
Right eye	18.13	14.6	-3.53
Left eye	20.62	14.18	-6.44

Table 2. Cross-sectional Area of Extraocular Muscles.

Cross-sectional area (mm ²)		Preoperative	Postoperative	Postoperative/Preoperative (%)
Superior rectus muscle	Right	84.5	54.56	64.5 (-35.5)
	Left	122.75	58.91	48.0 (-52.0)
Inferior rectus muscle	Right	37.37	35.54	95.1 (-4.9)
	Left	54.18	37.08	68.4 (-31.6)
Medial rectus muscle	Right	51.67	34.67	67.1 (-32.9)
	Left	49.54	39.01	78.4 (-21.6)

cancer (n=1), and malignant lymphoma (n=1). The histopathological type and stage varied among these patients. The major chief complaints were polyopia and reduced vision. Although most patients reported these symptoms several months prior to identification of the primary lesion, some developed eye symptoms after the diagnosis of their primary

lesions. In all previously reported cases, treatment of the primary lesion resulted in the improvement of the symptoms of exophthalmos. The symptoms improved in the majority of patients within days to months after the treatment of the primary lesions, which was consistent with our patient, who reported improvements in his symptoms approximately 10

Table 3. Case Reports of Exophthalmos as Paraneoplastic Syndrome (Including Our Case).

Reference	Age Sex	Pathology Stage	Chief complaints (time of onset prior to diagnosis of the primary lesion)	Treatments Clinical outcomes
3	43 years Male	Non-Hodgkin lymphoma (DLBCL) Stage IVA	Polyopia, conjunctival injection (3 months)	PSL: 100 mg+cyclophosphamide: 75 mg Symptoms improved within 3 months after the start of treatment
5	69 years Male	Lung cancer Squamous cell carcinoma (left) Stage IIIA	Exophthalmos (6 months)	Left lower lobectomy+lymphadenectomy Symptoms and swelling of the extraocular muscles were no longer observed postoperatively
2	51 years Female	Lung cancer Small cell cancer (right) Stage IIB	Exophthalmos (12 months)	Right lobectomy+partial chest wall resection Exophthalmos was no longer observed on postoperative day 10
4	65 years Male	Breast cancer (right) Stage unknown	Polyopia, reduced vision (unknown)	Right radical mastectomy Symptoms of ocular motility disorder improved 1 year after surgery
1	78 years Male	Lung cancer Adenocarcinoma (right) Stage unknown	Reduced vision (8 months)	Pemetrexed+bevacizumab+PSL: 20 mg Symptoms were no longer observed 10 days after the administration of PSL
Our case	75 years Male	Lung Cancer Pleomorphic carcinoma (left) Stage IIB	Polyopia (2 months)	Left upper lobectomy (parietal pleurectomy)+ segment 6 resection Subjective symptoms improved on postoperative day 10 Exophthalmos was no longer observed 2 months after surgery

DLBL: diffuse large B-cell lymphoma, PSL: prednisolone

days after treatment of the primary lesion and subsequent improvements in exophthalmos 2 months after treatment.

Previous studies have proposed several mechanisms to explain the development of exophthalmos in this context. They included abnormal activation of the immune system as a result of the anti-tumor response and the subsequent expression of inflammatory cytokines (1), as well as orbital swelling caused by the infiltration of immune cells and proliferation of fibroblasts around vessels in the extraocular muscles and orbital connective tissue (4). However, additional evidence will be required to clarify the mechanisms underlying the development of exophthalmos as a manifestation of paraneoplastic syndrome.

Conclusion

Paraneoplastic syndrome should be suspected if patients with malignant tumors present with exophthalmos without evidence of thyrotoxicosis. Treatment of the primary lesion is likely to improve the symptoms of exophthalmos caused by paraneoplastic syndrome.

The authors state that they have no Conflict of Interest (COI).

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