CASE REPORTS

Small Cell Lung Cancer and Cancer-Associated Retinopathy

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We report the case of a patient who presented with cancer-associated retinopathy and small cell carcinoma of the lung, which was treated surgically because the initial diagnostic biopsy finding was squamous cell carcinoma. The patient then underwent chemotherapy and radiation therapy. We discuss the characteristics and pathogenesis of this paraneoplastic syndrome as well as its association with the lung tumor's aberrant production of a protein that competes with retinal recoverin at the photoreceptors of the retinal cone.

Key words: *Cancer-associated retinopathy. Small cell lung cancer. Paraneoplastic syndromes.*

Carcinoma broncogénico microcítico y retinopatía asociada a cáncer

Se presenta el caso de un paciente afectado de una retinopatía asociada a cáncer, con un carcinoma microcítico de pulmón tratado quirúrgicamente, ya que la biopsia del diagnóstico inicial fue positiva para carcinoma epidermoide, y luego con quimio y radioterapia. Se analizan las características de este síndrome paraneoplásico, su mecanismo patogénico y su asociación con la producción anómala de una proteína por el tumor pulmonar que compite con la recoverina autóctona en los receptores de los conos retinianos.

Palabras clave: *Retinopatía asociada a cáncer. Carcinoma microcítico. Síndromes paraneoplásicos.*

Introduction

While the relationship between neurological paraneoplastic syndromes and small cell lung carcinoma is well documented in the literature, we believe that the following case report is of interest owing to the rarity of a case in which progressive blindness was the first sign of the neoplastic disease in a heavy smoker with a lung tumor that was still confined to the bronchial wall at the time of presurgical staging.

Case Description

The 66-year-old patient, a 40-pack-year smoker, had a history of atherosclerotic arteriopathy affecting the femoropopliteal and bilateral carotid areas, treated medically. He was admitted for investigation of his loss of color vision after a bilateral phakectomy without complications. His ophthalmologist indicated that the condition was a paraneoplastic syndrome and recommended a study to rule out the possibility of a tumor. The physical examination revealed a Karnofsky score of 80 with clinical evidence of disease. No evidence of disease was found by colonoscopy or gastroscopy. The only abnormality revealed by a posteroanterior chest radiograph was an enlarged left hilum (Figure 1). A 2.5-cm tumor lesion that did not take up the contrast material was detected by chest computed tomography in the posterior segment of the left lower lobe (Figure 2). The scan also evidenced small areas of subsegmental atelectasis in the same region and emphysematous changes in the upper lobes. No pathologically enlarged mediastinal lymph nodes were observed. No evidence of lesions was found in either the liver or the suprarenal regions. Bronchoscopy revealed an endobronchial lesion completely blocking the lumen in the posterior segment of the left lower lobe. Bronchial aspirate

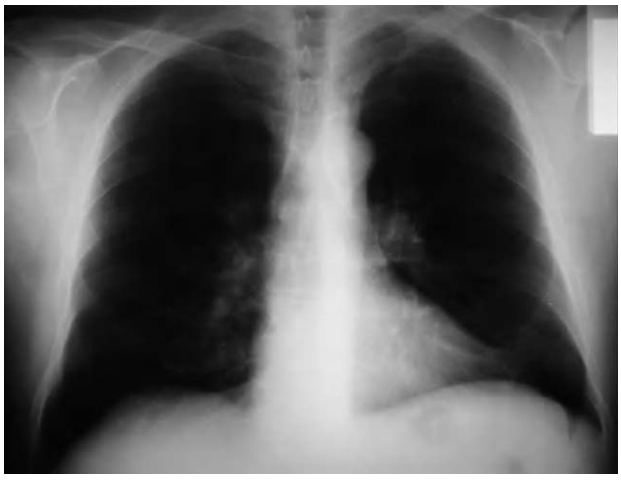

Figure 1. Preoperative posteroanterior plate showing no evidence of bronchial tumor.

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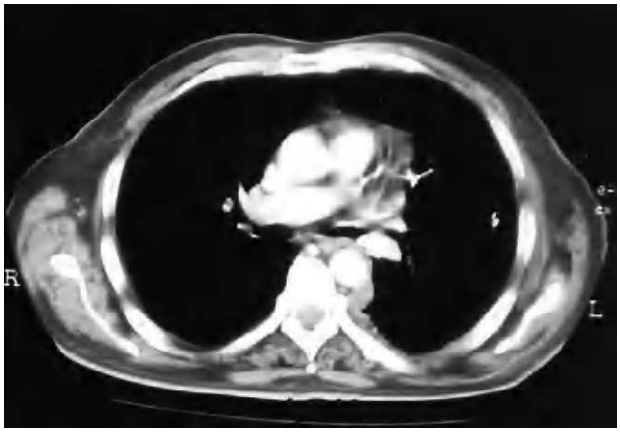

Figure 2. Chest computed tomography scan showing stenosis caused by a tumoral growth in segment VI of the bronchus.

cytology was positive for cancer, and a biopsy yielded a diagnosis of nonkeratinizing squamous carcinoma. The results of lung function tests were within the normal range, with a ratio of forced expiratory volume in 1 second to forced vital capacity of 2.58 to 3.54, around 80% of the predicted value. Arterial blood gases were normal. A scintigraphic bone scan detected no patterns consistent with metastasis.

The patient underwent a left thoracotomy; lower lobectomy and systematic node dissection were performed. The bronchus was sutured manually because tumor proximity made mechanical suture inadvisable. Intraoperative analysis of the bronchial stump detected no tumor invasion. Postoperative complications included a prolonged air leak and atelectasis of the upper left lobe which required repeated bronchial aspiration. The air leak stopped after 11 days of continuous drainage and therapeutic pneumoperitoneum. The patient was discharged 20 days after surgery.

The final pathology report on the excised tissue referred to an undifferentiated carcinoma of mixed small cells and large cells 2.1 cm in diameter. Two hilar nodes located very close to the tumor were affected. The mediastinal nodes were unaffected. The pathological staging classification of the tumor was pT1 pN1 pN0, stage IIA. No evidence of the presence of lesions consistent with metastasis was revealed by the postoperative computed tomography brain scan.

Surgical treatment was complemented by chemotherapy with cisplatin and etoposide for 3 cycles followed by radiation therapy targeting the mediastinum and the supraclavicular fossae. Subsequently, the patient received 3 further cycles of chemotherapy. No recurrence of the tumor was revealed by bronchoscopic and radiographic monitoring on follow up one year after surgery. The patient's ocular symptoms resolved gradually until he was asymptomatic. He was readmitted 28 months after the first operation with hepatomegaly and 2 subcutaneous nodules in the abdominal wall. Puncture of these nodules revealed neoplastic cells. Abdominal ultrasound confirmed metastases to the liver. The patient died at home while receiving palliative care 30 months after the operation.

Discussion

The association between a deterioration in visual acuity and lung cancer can be explained by the fact that both conditions achieve their highest frequency in people in their sixties. Consequently, coincidental detection of pulmonary lesions in the preoperative chest radiographs of patients scheduled for crystalline lens replacement operations is not unusual. The retinal retinopathy that occasionally accompanies cataracts is difficult to assess prior to the operation, and can be masked after the intervention by a complication secondary to the operation or by some other process. When color blindness is the only symptom and it is not accompanied by any other neurological signs suggestive of a paraneoplastic syndrome, the diagnosis of a primary tumor is extremely difficult unless the physician bears in mind the possible association of color blindness with a neoplasm. In general, vision problems caused by neoplasms are the result of metastases or tumoral invasion of the ocular region. The origin of such metastases is generally digestive or bronchial tract tumors in men and breast, digestive system, or ovarian tumors in women.[1,2] The most common site for uveal metastasis is the choroid, and it should be remembered that the symptoms reported by patients consulting their doctor because of vision problems are the first sign of distant disease in patients in whom ocular metastasis is subsequently found.[3-7] Tumors cause neurological paraneoplastic phenomena in different areas of the neural axis, and the mechanisms are diverse. The common characteristic is subacute onset, which may precede the appearance of the tumor, in some cases by a long period. Consequently the possibility of an occult tumor should be ruled out whenever such phenomena appear. Certain syndromes correspond to a particular type of tumor, and their incidence is well known, especially in small cell cancer of the lung (47%), stomach (12%), breast (12%), ovary (9%), and colon (6%). The pathogenesis of such syndromes can be found in an autoimmune response directed against certain common antigens expressed by the tumor and affected nerve cells. In small cell lung cancer, nuclear antibodies are produced that recognize the nuclear antigens of neurons, giving rise to paraneoplastic encephalomyelitis or a subacute sensory neuropathy. This response can cause lesions in more than one region of the neural axis, hence the importance of detecting these antibodies, the presence of which confirms the paraneoplastic origin of the process in question, even though the antibodies may not facilitate the diagnosis of a specific neurological syndrome.[8] In the case of paraneoplastic retinopathy, the determining factor is the presence of cancer-associated antiretinopathic antibodies against recoverin, a 23 kDa Ca2+ binding cone protein. The presence of such antibodies confirms the diagnosis of cancer-associated retinopathy. Another protein, in this case a 65 kDa heat shock protein, also participates in the mechanisms producing this type of blindness. The presence of antirecoverin antibodies, 23 kDa retinal proteins, indicates the paraneoplastic nature of the color blindness phenomenon and usually precedes the appearance of the symptoms related to the primary

tumor. Antirecoverin antibodies are produced in response to the recoverin aberrantly expressed by the tumor. These antibodies are then taken up by the photoreceptor cells and block the function of normal retinal recoverin (the inhibition of rhodopsin phosphorylation mediated by calcium), thereby giving rise to apoptosis.[9-11]

There are 2 types of cancer-associated retinopathy.[12,13] The retinopathy associated with small cell lung cancer is similar to pigmentary retinitis, whereas that associated with melanoma is less well known and has been studied less. Neurological disease associated with small cell cancer has been studied extensively and is associated with a considerable number of neurological phenomena related to the production of antibodies provoked by the primary tumor. The most well known of these conditions are cerebellitis, limbic encephalitis, opsoclonus myoclonus syndrome, stiff-person syndrome, and Lambert-Eaton myasthenic syndrome, with antibodies against calcium channels, potassium channels, and recoverin.[14,15] Recoverin, which is expressed aberrantly by lung tumors, is the antigen that triggers the production of the antirecoverin antibodies which subsequently block the function of normal retinal recoverin.[16,17] It has been established that the gene associated with recoverin is located on the short arm of chromosome 17 at position p13.1 close to other cancer-related loci that would give rise to retinopathy.[18] However, a recently published article reported recoverin production by small cell tumors that did not trigger the appearance of cancer-associated retinopathy.[19]

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