Stabilization of metastatic myxopapillary ependymoma with sorafenib

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Abstract

We report on a 59-year old woman with three huge intrathoracal masses that were accidentally diagnosed when she consulted a physician for upper abdominal discomfort. A biopsy revealed that they were metastases of a coccygeal myxopapillary ependymoma, resected 20 years before. As neither resection, debulking, nor radiation therapy were considered to be indicated, systemic therapy with temozolomide was started. At the first evaluation after four months, the metastases had progressed. Imatinib delayed the progression, but had to be stopped after six months because of critical increased pleural effusion. Using the multikinase inhibitor sorafenib, the disease was stabilized and an acceptable quality of life could be obtained for one year.

Introduction

Most ependymomas are benign neoplasms originating from the ependymal glia, the inner glial layer lining cerebral ventricles, the aqueduct and the central canal of the spinal cord. They are mostly benign and grow slowly. In the last 50 years, ependymomas with distant metastases have been described, but they remain exceedingly rare. Most of these metastasizing tumors are of intracerebral origin and only a small number are located in the spinal cord or extraspinal. Because of its rarity, we think it is of importance to describe our 59-year old patient with huge pulmonary metastases diagnosed 20 years after the resection of the primary sacrococcygeal tumor, a myxopapillary ependymoma. As local therapies were deemed futile, this patient posed a great challenge when her performance status deteriorated so that systemic therapy was needed. We report the course of therapy of this patient.

Case Report

The female patient (born 1952), had undergone surgery for the removal of a coccygeal tumor at the age of 37 years in a small community based hospital. The tumor had caused a peroneal nerve dysfunction. The histological examination of the encapsulated mass, measuring 6.5×5.5×4 cm, revealed a myxopapillary ependymoma. The pathologist described cuboid monomorphic glial fibrillary acidic protein positive cells, arranged in the perivascular space or papillary around a hyalinized central core, with rosettes, microcystic areas and a noticeable mucinous obstruction. A thin fibrous capsule surrounded the sharply delimited nodule, the typical findings of a myxopapillary ependymoma World Health Organization (WHO) grade I. It was not established whether it originated from the filum terminale or from the cauda equina.

Six years later, a local recurrence at the os coccygis was resected in another community based hospital. The resected recurrent tumor consisted of a mass measuring 12×6×6 cm, including a 2.5 cm long part of the os coccygis and a 12×6 cm skin flap. There were two nodules with, respectively, a 4 and 5 cm diameter direct caudal of the os coccygis and one small 0.5 cm subcutaneous nodule on the left side of the bone. At histological examination, the nodules showed the typical picture of a myxopapillary ependymoma, without increased mitotic activity. The reaction with an antibody against cytokeratin was negative. The skin was not infiltrated; the resection margins and the os coccygis were free of tumor. The pathologist confirmed the diagnosis of extraspinal myxopapillary ependymomas and mentioned occasional distant metastases occurring in the lung or in inguinal lymph nodes.

Fourteen years later, in 2009, the patient again underwent a computed tomography (CT) scan because of upper abdominal discomfort. Unexpectedly, three pleural polylobulated, heterogeneous enhancing masses were described in the lungs: in the recessus costo-mediastinalis of the right side (12×7×11 cm), in the left recessus paravertebralis (6×6×10 cm) and aorto-pulmonal (5×8×8 cm), as well as a smaller nodule of 16 mm in diameter in the left lung, and a small, encapsulated pleural effusion of the left side (Figure 1A). The patient underwent transthoracal needle biopsy of the right pleural mass which confirmed that the intrathoracal masses were indeed metastases of the ependymoma diagnosed 20 years previously. Subsequent 18F-FDG-PET/CT imaging (F-18 fluorodeoxyglucose positron emission tomography computed tomography scan) showed the same three tumor masses and revealed no further FDG-enhancing regions. At this time, the patient was clinically symptom free.

She was referred to the tumor board at the Medical University of Vienna for discussion of potential treatment options. Because of the huge tumor masses and the involvement of aortopulmonal vessels, surgery was declined and radiotherapy was not considered meaningful due to the extension of the potential radiation fields. As the patient was symptom free and in a very good performance status (WHO grade I), a *wait and see* policy was proposed. Four months later, the patient complained of dyspnea on exertion. A spiral CT scan of the thorax revealed progression of the pleural and pulmonary metastases and an increase in the pleural effusion (Figure 1B). Systemic therapy with dose-dense temozolomide (100 mg per day, five days of a weekly cycle) was started. But after three months, a clear progression with increasing dyspnea and pain mainly of the left hemithorax was reported. The metastases had progressed again (Figure 1C). Therefore, in December 2009, temozolomide was stopped and imatinib (400 mg daily) was initiated because according to immunohistochemistry the tumor cells of the biopsy were reactive to anti-PDGFR-. One month later, the pleural effusion had increased, but the CT scan showed that the metastases were slightly reduced (Figure 1D). As effusions are a well-known side effect, imatinib was temporarily stopped to allow the decline of the pleural effusions and then reintroduced after three weeks. However, the next CT scan again showed a further increase in the pulmonary masses (Figure 1E). Therefore, in May 2010, the systemic therapy was changed to sorafenib. The patient experienced several side effects of WHO grade I that reversed spontaneously (scaly skin, aphthes and films in the oral cavity, paraesthesias, headache and hoarseness). But her clinical condition improved and the tumor masses stopped growing (Figure 1F). However, in April 2011, sorafenib was stopped due to a mixed axonal demyelinating polyneuropathy (Figure 1G) which impaired gait.

Discussion

Ependymomas are glial tumors, arising from the wall of the ventricles or from the spinal canal. They are rare primary central nervous system

tumors in adults. They may occur either in the brain, where they account for 1-3% of primary brain tumors, or in the spinal cord, where they represent approximately 63% of tumors, or extraspinally. Myxopapillary ependymomas were first described by Kernohan in 1932 and occur preferentially in the conus medullaris/cauda equine region, although there are reports of myxopapillary ependymomas in the brain,[1] the upper spinal cord and (in very rare cases) extraspinally.[2] Outside the central nervous system, they mostly occur in the sacrococcygeal subcutaneous tissue or the presacral regions.[3] Exceptional cases of myxopapillary ependymomas have been reported as primary tumors of the os sacrum,[4,5] in

the ovary,[6] the uterine ligaments and the mediastinum.[7,8] Proposed etiologies for extradural development include direct extension through the dura, heterotopic ependymal cell nests,[9] and extradural remnants of the filum terminale.[2,10] A germ cell origin has also been proposed, which may explain the occurrence in the ovary and mediastinum.

Ma *et al.*[2] compiled a review of 75 reported cases of extraspinal ependymomas. They stated that, although the patients ranged from two months to 67 years of age, most of the published cases of sacrococcygeal ependymomas occurred in children and young adults. Sonneland *et al.*[11] found that the mean patient age at presentation

was 36.4 years. This finding is in accordance with our patient, who was aged 37 years at resection of the primary tumor. Whereas Sonneland *et al.* found a slight male predilection, according to Ma *et al.*,[2] the male to female ratio in affected individuals is roughly equal.[2]

Nearly all sacrococcygeal myxopapillary ependymomas cause low back pain. Other manifestations, such as sciatic pain, sensomotor deficits, impotence, and urinary and fecal incontinence, are much less common. The first symptom our patient presented, and which led to the detection of her coccygeal tumor, was a peroneal nerve palsy. Expecting a teratoma, the surgeon resected the encapsulated mass *in toto*. But the
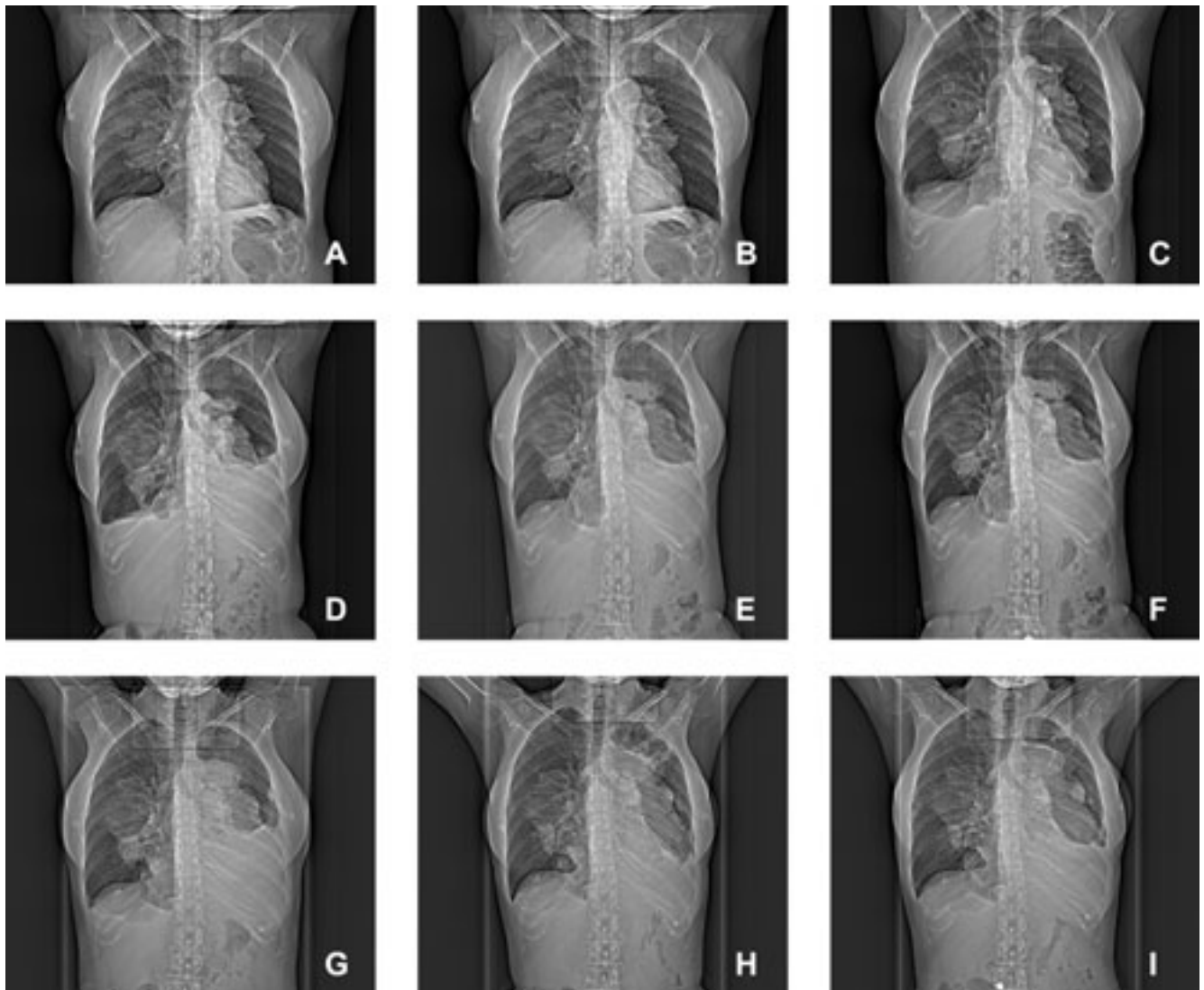

Figure 1. Coronal computed tomography scan overview of the patient's thorax with metastasized myxopapillary ependymoma. Findings and clinical symptoms: A) three pleural masses and multiple pulmonary nodules, a small encapsulated pleural effusion on the left side; B) progression of intrapulmonary nodules and of the pleural effusion on the left side; C) progression (dyspnea on exertion, thoracal pain, weight loss); D) progression of pleural effusion (dyspnea at rest); E) decrease of pleural effusion, but increase of tumor masses (hoarseness); F) stable disease (dry skin, paraesthesias, hoarseness, aphthes and films in the mouth, pain); G) stable disease (sleep disturbances, pain, hypertension); H) stable disease (weakness); I) stable disease (weakness and mixed axonal polyneuropathy in 3/11). Antineoplastic therapy: start temozolomide (B), start imatinib (C), reinduction imatinib (E), sorafenib (F), dose reduction because of suspect metastases in the spinal cord, reinduction of the full dose (G), sorafenib ongoing (H, I).

histological examination revealed a myxopapillary ependymoma. Even so, the patient had the treatment of choice: complete resection, while maintaining capsule integrity. This was repeated at the time of local recurrence six years later.

Intradural lumbosacral ependymomas can spread throughout the central nervous system but only rarely metastasize outside this. Similarly, extradural ependymomas rarely disseminate within the central nervous system, but pose a certain risk for systemic metastases.[12,13] However, the rate of distal metastases of myxopapillary ependymomas has been reported in the range of 18-27%, with the lungs as the most common site of spread, followed by the pleura, the thoracic and abdominal lymph nodes, and the liver.[14,15] Distant metastases can develop decades after initial presentation.[10,15]

This was the case with our patient as pulmonary metastases had been found incidentally 20 years after the primary diagnosis. Because of the huge tumor masses, neither surgery nor radiotherapy was considered adequate treatment. Therefore, potential options for systemic therapy were evaluated. Cytotoxic chemotherapy has not been studied extensively in myxopapillary ependymomas. Furthermore, there are no guidelines for chemotherapy of ependymomas. Platinum based and nitrosurea based regimens showed very modest effects in the setting of recurrent disease.[16,17]

There are some previous reports on the use of temozolomide (TMZ) in patients with ependymomas. In a retrospective study of 25 patients with recurrent ependymomas, TMZ demonstrated little efficacy.[18] However, Kim *et al*.[19] reported a long lasting response of 20 months in a patient with a malignant ependymoma. In contrast, in the case of our patient, a short course of dose-dense TMZ was found ineffective.

Since cytotoxic chemotherapy did not appear to be appropriate for our patient's slowly growing tumor, the idea of inhibiting specific molecular pathways was a more attractive option.

As immunohistochemistry had shown expression of the platelet derived growth factor receptor alpha, imatinib was the first drug of choice. Furthermore, our personal experience with imatinib in an adult patient with recurrent spinal ependymomas was favorable.[20] However, the patient discussed in this case report showed quite poor tolerance of imatinib. In addition, the metastases progressed considerably.

Sorafenib, a multikinase inhibitor affecting tumor growth and angiogenesis by inhibiting intracellular RAF kinases and cell surface kinase receptors (VEFGR 2-3, PDGFRb, cKIT, FLT-3) was the next strategy. It was attractive due to its target profile, manageable toxicity profile and its oral availability. With this drug, the disease was stabilized for a year. But after this prolonged use of sorafenib, the patient increasingly experienced gait disturbance and muscular weakness mainly of the proximal musculature. The symptoms worsened and, therefore, by March 2011, the patient was nearly immobile and had lost weight. A neurophysiological examination revealed a mixed axonal demyelinating polyneuropathy with toxic causality (Figure 2). We found no report for
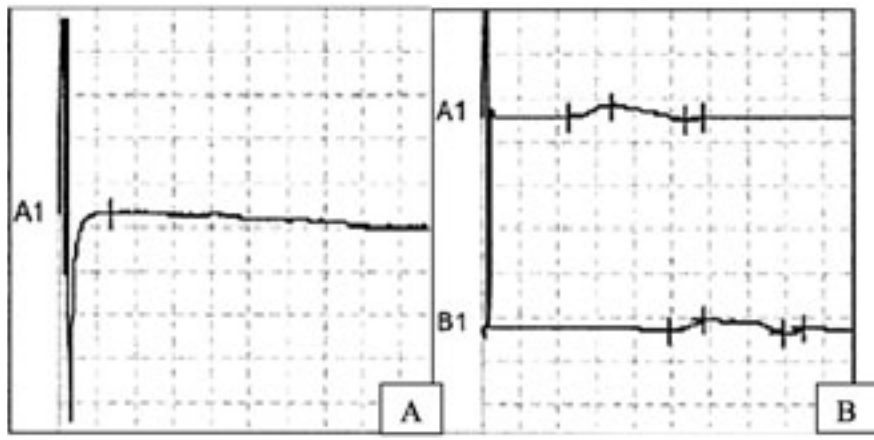

Figure 2. Electromyogram/nerve conduction study: decrease of amplitude and diminution of motoric nerve conduction velocity of the right (A) and left (B) *N. peronaeus* in March 2011.

sorafenib inducing this form of neuropathy; only sensory forms are mentioned in the literature.[21] After stopping sorafenib, the neuropathy slowly improved.

Conclusions

Extradural ependymomas must be considered in any differential diagnosis of pre- and post-sacral mass lesions, and complete surgical removal should be attempted in all cases. As recurrence and metastases can develop after an extended disease-free interval, a careful life-long follow up is required for patients with extradural myxopapillary ependymoma. The low incidence of this tumor limits the possibility of large prospective clinical trials. Case reports are a way to share experience and develop strategies. However, collecting case studies and data, even for uncommon conditions, in a multinational register would be highly welcome.

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