

Bone marrow metastases from anaplastic oligodendroglioma presenting with pancytopenia and hypogammaglobulinemia: a case report

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ABSTRACT

We report the case of a 40-year-old man whose bone marrow metastases occurred 57 months after the initial diagnosis and 9 months after completing radiotherapy for an anaplastic oligodendroglioma. Four months before the demonstration of visceral metastases was obtained by bone marrow biopsy, the patient developed diffuse bone pain, pancytopenia, hypercalcemia, and panhypogammaglobulinemia. These abnormalities and other clinical signs of extracranial dissemination of the primary brain tumor were initially unrecognized until the patient was admitted with the suspicion of a nonsecretory multiple myeloma. We also briefly review the factors predisposing these tumors to spread outside the CNS, albeit rarely, and discuss the clinical implications of a misdiagnosis of extracranial invasion by anaplastic oligodendroglioma, whose chemosensitivity has been definitively demonstrated.

Introduction

Oligodendrogliomas (ODs) are uncommon neoplasms accounting for about 5% of all primary brain tumors¹⁻³. They are predominantly tumors of the adult, with a peak incidence between the fourth and sixth decades of life. Low-grade ODs tend to arise in slightly younger patients. Although patients with low-grade ODs in particular may have a median survival time of more than 10 years, the outcome is almost invariably fatal. Systemic metastases from these neoplasms have rarely been described in the medical literature^{2,4}. The overall survival of patients with this condition is increasing, possibly due to advances in its early detection and in surgical technique, diagnostic imaging, histological and molecular diagnosis, chemotherapy and radiotherapy^{1,5,6}.

What prompted the present report was the observation of a man whose bone marrow metastases occurred 57 months after the initial diagnosis and 9 months after completing radiotherapy for an anaplastic OD. The signs and symptoms of the bone marrow metastases first went unnoticed and then were believed to be due to a nonsecretory multiple myeloma. We also briefly review the factors predisposing these tumors to spread outside the CNS, albeit rarely, and discuss the clinical implications of a misdiagnosis of extracranial invasion by anaplastic oligodendroglioma, whose chemosensitivity has been definitively demonstrated⁵.

Case report

In December 1997 a 40-year-old man first presented with a single grand mal fit. Cranial CT scan demonstrated a probable OD of 3 cm in diameter in the left opercular gyrus. He was maintained on phenobarbital and was well until December 2000, when he suddenly awoke with morning headache. CT scan showed that the diameter of the contrast-enhanced mass had increased to 5 cm. In February 2001, he underwent a craniotomy with subtotal resection of the mass, which was found to have the histolog-

Key words: bone marrow biopsy, bone marrow metastases, oligodendroglioma, myeloma, pancytopenia.

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Received October 4, 2010;
accepted December 1, 2010.

ical features of anaplastic OD. At that time there were no clinical or radiological signs of extraneural metastases. Postoperative radiotherapy was administered for a total dose of 50 Gy in 35 fractions in October-November 2001. In August 2002, the patient suffered from lumbar pain, weakness and weight loss. No correlation between the patient's symptoms and the primary tumor was suspected and no other diagnostic procedures were performed. In the following months, the lumbar pain progressively extended to diffuse bone pain. In December 2002, he was admitted to our department with a clinical suspicion of a nonsecretory multiple myeloma because of his concomitant pancytopenia, panhypogammaglobulinemia, mental confusion, hypercalcemia, diffuse bone pain, bradykinesia, and weight loss. Physical examination showed a severely ill, lethargic man, unable to deambulate without assistance. The liver and spleen were both palpable 3 cm below the costal margin. There were no palpable superficial lymph nodes. A complete peripheral blood count gave the following values: WBC $3.9 \times 10^9/L$, RBC $2.3 \times 10^{12}/L$, Hb 71 g/L, Ht 20.8%, MCV 94 fL; MCH 30.3 pg/L, platelets $57 \times 10^9/L$. Altered serum biochemical parameters included ESR 105 mm, AST 98 U/L, ALT 304 U/L, γ GT 1602 U/L; calcium 12.4 mg/dL, phosphorus 5.7 mg/dL. Serum PTH was undetectable. The patient had panhypogammaglobulinemia with IgG 4.6 g/dL, IgA 0.36 g/L and IgM 0.71, with a polyclonal pattern on immunofixation. Serum proteinemia, albuminemia, urinalysis and creatinine were in the normal range. Bence Jones proteinuria was absent. A contrast-enhanced CT scan and gadolinium MRI of the brain showed a cystic lesion in the frontal lobe with no signs of any local recurrence of the original tumor. MRI of the spine was normal. Abdominal CT scan revealed hepatosplenomegaly without focal lesions, enlarged retroperitoneal and perirenal lymph nodes, and a mass of 2.2 cm in diameter in the left adrenal gland. Bone marrow biopsy showed complete effacement of normal bone marrow elements by a diffuse infiltrate of non-hemopoietic cells consistent with OD; there were diffuse areas of necrosis. The infiltrating cells were immunohistochemically positive (data not shown) for enolase and glial fibrillary acid protein (GFAP) and negative for CD20, CD138, MPO, keratin and neurofilaments. Non-hemopoietic cells were also clearly visible in samples prepared from bone marrow aspirates (Figure 1).

The patient was started on pamidronate, steroids and chemotherapy with procarbazine, lomustine and vincristine, but after 1 cycle he progressively deteriorated and died 2 weeks later, about 4 months after the clinical presentation of the bone marrow metastases.

Discussion

Distant metastases from brain ODs have been considered rare^{4,7-9}. Among the extraneural sites, bone marrow

is the most often affected by invasion from these tumors in both adults⁴ and children¹⁰.

The presence of the blood-brain barrier, the absence of lymphatics within the CNS, the short survival of these patients, the inaccessibility of the venous system to the neoplastic cells, the host's immune response and possibly also some biological features of the transformed cells are believed to be the main barriers to the spread of gliomas outside the CNS^{7,10-15}. On the other hand, the conviction that systemic invasion is so rare may mean that this possibility is sometimes overlooked and that specialists are misguided in their diagnoses, thus giving rise to an erroneously low incidence of distant metastases, whereas the picture might be different if more appropriate diagnostic procedures were performed¹².

Conversely, a lengthy survival, multiple craniotomies, and shunts are thought to predispose patients to metastasis^{12,14}. Given the demonstrated chemosensitivity of anaplastic OD^{5,16}, we might expect an increasing rate of long-term survivors and consequently metastases – if longer survival really is an important risk factor for systemic metastases and extraneural dissemination^{7,17,18}.

Long-term survival was the only risk factor for tumor spread in our patient: he survived 61 months after the initial diagnosis of brain OD, 22 months after the only craniotomy he underwent, 11 months after completing radiotherapy, 4 months after the clinical onset of bone marrow metastases, and about 2 months after the histological confirmation of bone marrow metastases.

There are discordant points of view in the literature regarding the longer survival of patients with distant metastases from OD compared with patients without metastases, possibly because the patients included in clinical series varied in their diagnoses and treatment received¹. The mean survival of patients with these tumors is 4-5 years^{1,14}, but Macdonald *et al.*², in their review of 15 cases of bone marrow metastases from OD reported up to 1989, observed a shorter median survival (about 29 months) in patients with OD metastasizing to bone marrow than in those without systemic dissemination. Others have reported a shorter survival for patients without metastases or a comparable survival between the 2 groups of patients².

The diagnosis of bone marrow metastases was made after some delay in our patient, mainly because the link between the patient's signs and symptoms and his original brain neoplasm was not recognized. If the biopsy had not been performed, it would probably have been taken for granted that the patient had developed a disseminated second primary tumor¹⁰ or other systemic disorder.

Unfortunately, no autopsy was performed in this case, so we can only speculate on the nature of the hepatosplenomegaly and other abnormalities revealed by abdominal CT scan, and on whether there was genuinely no local brain tumor recurrence, as suggested by the MRI and CT scan. Although bone marrow biopsy is not

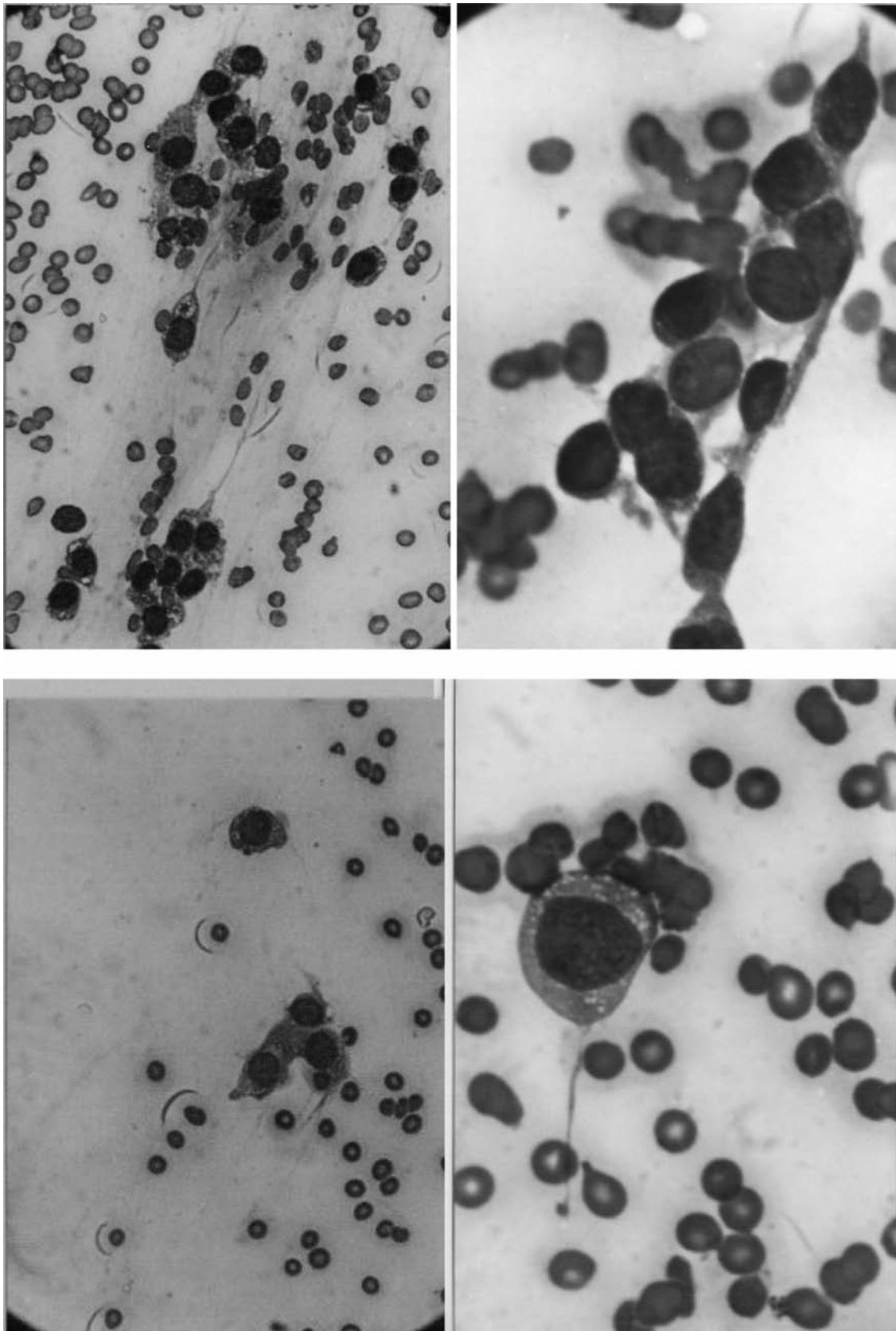


Figure 1 - Giemsa-stained smears from sternum bone marrow needle biopsy showing clusters of neoplastic nonhematopoietic cells with round nuclei and abundant cytoplasm with projections.

routinely performed in patients with OD, also in our opinion it would make sense to apply this simple procedure to selected patients who present with bone pain and unexplained peripheral blood cell abnormalities^{10,17,19}. Bone marrow aspiration, generally performed as part of a trephine biopsy²⁰, may show, as it did in our case (Figure 1), metastatic tumor and should be taken into account as a complementary investigation²⁰.

Bone marrow and other systemic metastases may not be as rare as was previously thought, and they probably are a late event in the course of the disease²¹. Moreover, they respond to chemotherapy, so an early diagnosis is mandatory to improve the prognosis for these patients. We cannot reasonably rule out the possibility that an earlier diagnosis of the bone marrow metastases and earlier chemotherapy might have changed the poor prognosis in our patient.

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