Long-Term Survival in High-Grade Axial Osteosarcoma With Bone and Lung Metastases Treated With Chemotherapy Only

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Summary: A boy, age 2 years 10 months, with high-grade malignant osteosarcoma of the fifth lumbar vertebra with secondary bilateral pulmonary lesions and bone metastasis at the fifth thoracic vertebra is described. The primary site of disease was inoperable and the patient was treated with chemotherapy only. At present, 83 months from diagnosis and 64 from the end of therapy, he is in very good general condition. Although a surgical approach on the primary and secondary sites is fundamental, this case may be considered an indication of the efficacy of aggressive chemotherapy in treating osteosarcoma.

Key Words: osteosarcoma, chemotherapy, childhood

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The prognosis for osteosarcoma patients has greatly improved in recent years. Chemotherapy, associated with surgery some 30 years ago to treat osteosarcoma, has improved the survival in patients with limb tumors from 10% to 20% to today's 70% to 75%.[1–6] Despite encouraging improvements in survival rates for localized forms, however, the prognosis is still poor for patients with metastasis at presentation, particularly in case of bilateral pulmonary metastases or bone secondary lesions, and for patients with an axial localization of disease, which is often correlated with an increased potential for metastasis due to the frequent presence of a large tumor mass and the impossibility of surgical removal.[7–13]

We describe a boy (2 years 10 months old) diagnosed with high-grade malignant osteosarcoma of the fifth lumbar vertebra with secondary bilateral pulmonary lesions (three nodules) and bone metastasis at the fifth thoracic vertebra. The site of the tumor and the child's age made surgery impractical and the patient was treated exclusively with chemotherapy according to the ISG-SSG II protocol. To our knowledge, as no similar case could be found in a meticulous search of the literature, this case may be worthy of attention.

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CASE REPORT

In May 1997 a child (2 years 10 months old) with a 2- to 3-month history of pain in the right leg came to our attention: in the past 2 months there had been general weakness and hyposthenia in the legs. A painful, hard, 5-cm-diameter tumefaction was evident in the right paravertebral site at the sacrolumbar joint. A CT scan of the abdomen and pelvis revealed a lithic area with soft sclerotic edges on the right side at the top of the fifth lumbar vertebra and an increase in size of the psoas muscle, which was roundish and hypodense, with well-defined, slightly patchy edges. A similar formation for densitometric characteristics was observed in the homolateral iliocostalis muscle (Fig. 1). Radiography of the spine showed a secondary lesion of the fifth thoracic vertebra, with a sharp wedge-shaped depression of the vertebra and tissue neoformation that slightly exceeded the somatic edges. A chest CT scan showed one hyperdense nodule at the posterobasal segment of the lower right lobe and two nodules on the left, with a maximum diameter of 7 and 5 mm, respectively, at the top of the lower lobe and close to the great interlobar fissure (Fig. 2). Total body bone scintigraphy with Tc 99-MDP revealed hypercaptation of the primary site. Magnetic resonance imaging of the spine confirmed secondary disease of the fifth thoracic vertebra, which had similar radiologic characteristics to the primary lesion (Fig. 3). Blood chemistry and other laboratory findings (including calcium, phosphorus, alkaline phosphatase, lactic dehydrogenase, and sedimentation rate) were all within normal ranges. Urine homovanillic acid, vanilmandelic acid, dopamine, adrenaline, and noradrenaline levels were normal.

An open biopsy was made at the fifth lumbar vertebra. The histologic examination, carried out by the surgical pathology department of the Rizzoli Orthopaedic Institute of Bologna, led to the diagnosis of a quite undifferentiated round/oval cell tumor with osteoid matrix, classifiable as highly undifferentiated osteosarcoma, osteoblastic type (Fig. 4). This diagnosis was confirmed by Dr. K. K. Unni from the Mayo Clinic. The immunohistochemistry evaluation showed that the round cells were positive only for vimentin and were negative for cytokeratin A and B, epithelial membrane antigen, actin G and L, sarcomeric actin, chromogranin, synaptophysin, and CD 99. Bilateral bone marrow aspirates showed no evidence of disease.

The patient has been undergoing treatment at the Pediatric Oncology Department of the University of Turin since June 1997. Due to the severity of the case with the axial localization of the primary tumor and the presence of multiple bilateral pulmonary metastases and the secondary bone lesion, the patient was enrolled in the treatment program according to the ISG-SSG II protocol, elaborated by the Italian and Scandinavian Sarcoma Group for cases of high-grade malignant metastatic osteosarcoma and/or with disease

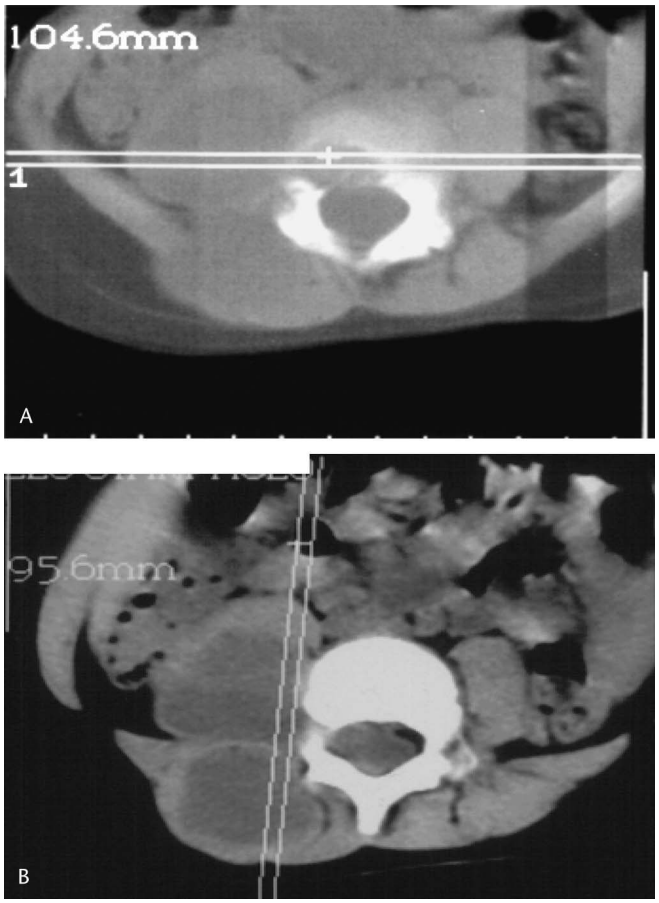

FIGURE 1. CT scan of primary site at diagnosis.

of the pelvis. The intended treatment plan included a preoperative phase with the four most active drugs (methotrexate, cisplatin, doxorubicin, and ifosfamide) in osteosarcoma, followed by surgery on the primitive and secondary lesions (which was, however, not carried out), and postoperative chemotherapy with doxorubicin, cyclophosphamide, and etoposide and two cycles of carboplatin and etoposide with previously harvested peripheral blood stem cells (PBSCs).

The patient received preoperative chemotherapy with methotrexate 12 g/m^2 intravenously for 4 hours continuously on days 0 and 42 with folinic acid rescue, cisplatin 120 mg/m^2 intravenously for 48 hours continuously from day 7 and 49, doxorubicin 75 mg/m^2 intravenously for 24 hours continuously from day 9 and day 51, and ifosfamide 15 g/m^2 intravenously for 120 hours continuously from day 28 and day 70. There was a rapid response to therapy and prompt regression of the painful symptoms and hyposthenia of the lower limbs. After the first chemotherapy cycles the paravertebral swelling was no longer visible. Re-evaluation at the end of preoperative chemotherapy showed a marked reduction of the paravertebral soft tissue involvement and the disappearance of one of the pulmonary nodules. Surgery was considered impractical. Two cycles of doxorubicin 90 mg/m^2 intravenously for 24 hours continuously were administered, intercalated by one cycle of cyclophosphamide 4,000 mg/m^2 and etoposide 600 mg/m^2 and followed by two consecutive high-dose cycles of carboplatin (1,500 mg/m^2) and etoposide (1,800 mg/m^2) over 4 days with reinfusion of PBSCs, harvested after the second cycle of ifosfamide in the preoperative phase and after the postoperative cycle of cyclophosphamide and etoposide. Three aphereses were performed, with collection of 10.25 $\times$ 10^6/kg CD34+ cells.

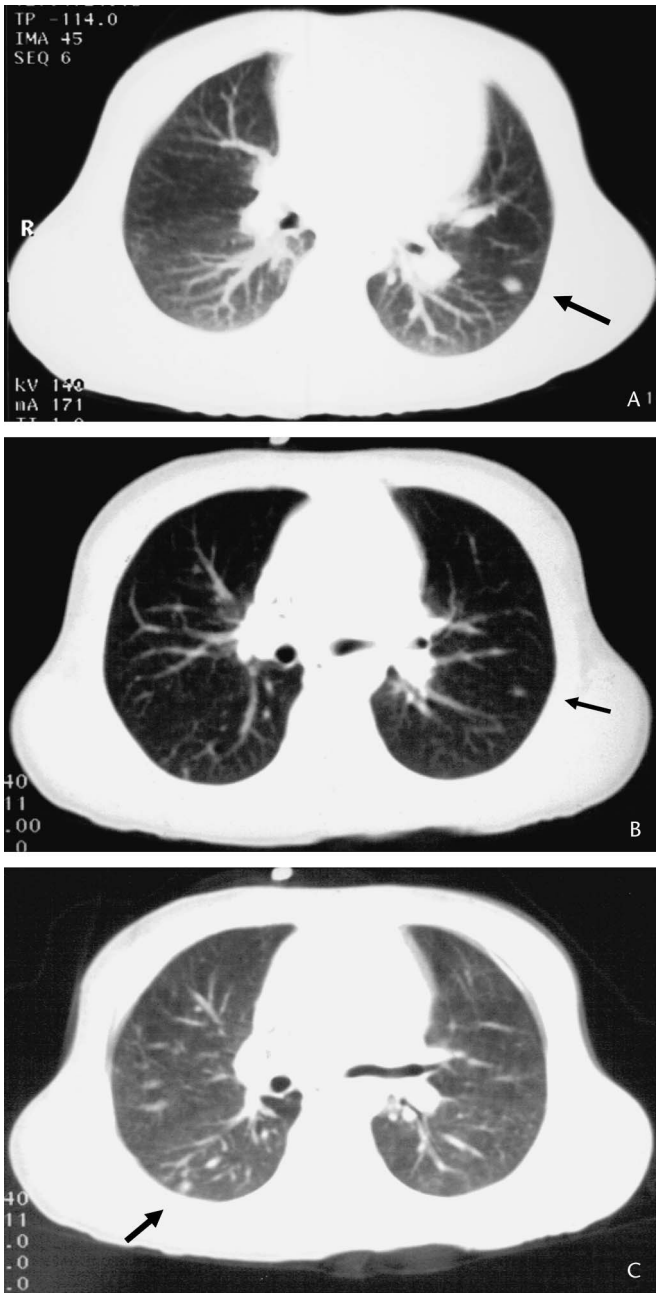

FIGURE 2. Lung CT scan at diagnosis.

Supportive treatment with granulocyte colony-stimulating factor (G-CSF) 5 mg/kg/d was administered after each course of chemotherapy, with the exception of methotrexate. G-CSF 10 mg/kg/d was used after mobilizing cycles to harvest PBSCs.

Chemotherapy was well tolerated with sufficient hematologic recovery even after the two high-dose cycles of carboplatin and etoposide. Platelets reached values of more than 25,000/mL 10 and 12 days after the first and second cycle, respectively. The absolute neutrophil count exceeded 500/mL after 9 days from the first cycle and 11 days from the second one. No hepatic, renovesical, or neurologic toxicity was observed.

Posttreatment imaging has shown good control of the bone and soft tissue lesions, with complete disappearance of the pulmonary nodules. The option to operate was discussed a number of times but

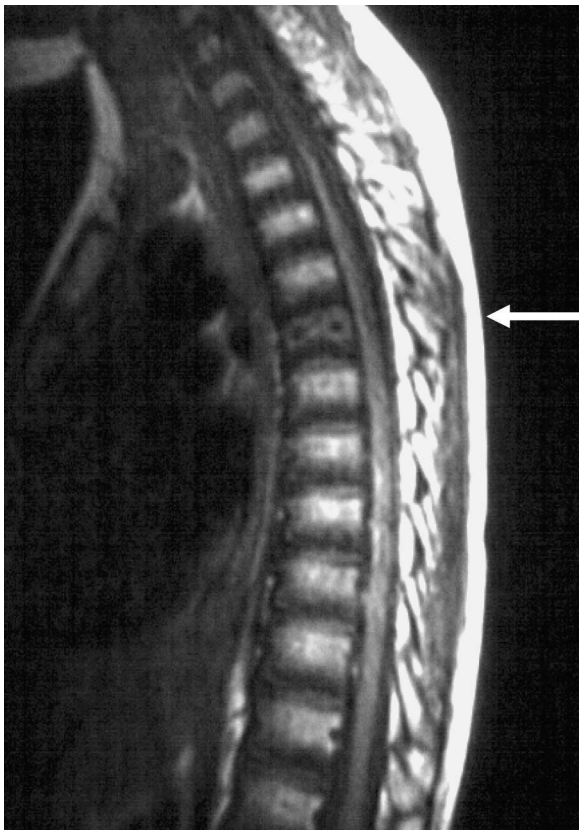

FIGURE 3. Spinal MRI at diagnosis (fifth thoracic vertebra).

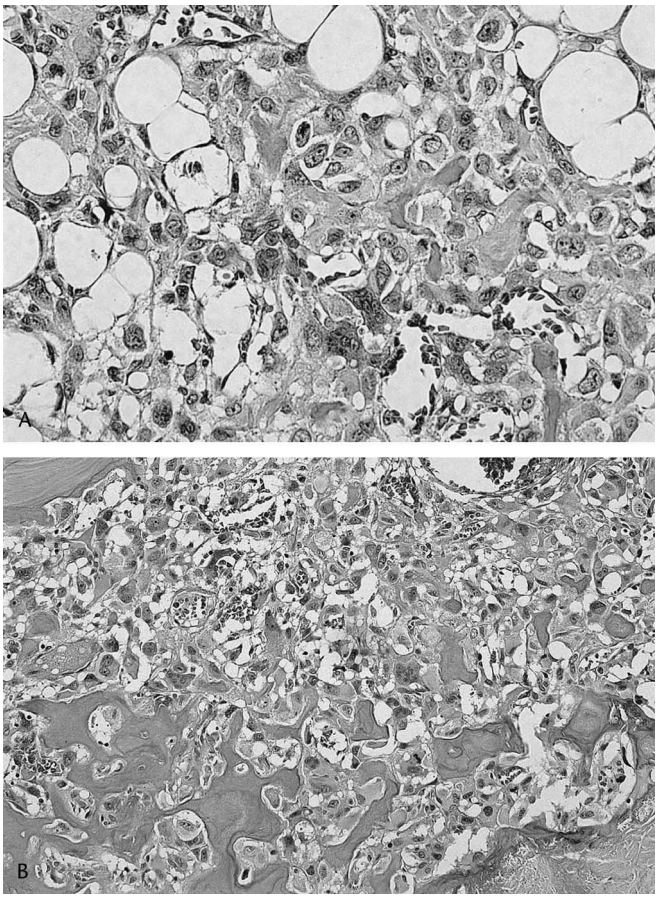

FIGURE 4. A, Highly undifferentiated sarcoma: oval/spindle cells with hyperchromatic nuclei and scant cytoplasm are embedded in a hyaline stroma with osteoid production (H&E, 300×). B, Highly undifferentiated sarcoma with immature and irregular osteoid trabeculae produced by the undifferentiated small cells: grade 4 osteoblastic osteosarcoma (H&E, 250×).

was held to be impractical because of the site of the tumor and the patient's age. Also considered was whether to carry out a needle biopsy or open biopsy of the residual tumor, which imaging evaluation interpreted as fibrotic tissue. However, as the tumor was not homogeneous, obtaining a sufficient histologic sample of the whole residue would have proved difficult.

The patient was in a good general condition, the control of the lesions was good, chemotherapy was well tolerated, and therefore we decided on a further three cycles of methotrexate 12 g/m^2 followed by etoposide 50 mg/m^2/d orally for 21 days per month, for a total of 12 cycles. The choice of radiotherapy was not made in light of the patient's age and the possibility of serious sequelae in case of adequate doses.

After therapy there were various elements in favor of the fibrotic nature of the residue. Total body bone scintigraphy with Tc99-MDP was within normal ranges; CT scan of the spine showed the tumor to be stationary, with no enhancement after contrasting the soft tissues; compared with the sequences carried out at diagnosis, MRI of the spine showed a clear reduction of signal in the T2 sequence, with a large reduction of the part involving the medullary canal. At present, 83 months from diagnosis and 64 from the end of therapy, the patient is in good overall condition, thoracic CT scan and total body bone scintigraphy with Tc99-MDP and PET-CT are normal, and MRI of the spine remains unchanged since the end of therapy, with morphostructural alterations of the spine at the fifth lumbar vertebra and the fifth thoracic vertebra.

DISCUSSION

The prognosis for osteosarcoma patients has greatly improved over the past 30 years thanks to improvements in surgical techniques and the introduction of aggressive chemotherapy, including cisplatin, doxorubicin, methotrexate, and ifosfamide, with the possibility for systemic and local control of disease. Until the 1970s, patients were treated with surgery alone, with success rates in the region of 10% to 20%.[1] Later, chemotherapy plus surgery was introduced. The first protocols included surgery plus postoperative chemotherapy with a considerable improvement in survival but a high percentage of amputations.[1–4] From the mid-1970s, the introduction of neoadjuvant chemotherapy made it possible to carry out limb-salvage procedures without increasing the percentage of local relapse. In patients who responded, cytostatic drugs helped control of local and systemic disease, thus sterilizing micrometastases that could not be detected with imaging techniques but that were deemed to be present at diagnosis in 80% to 90% of patients.[6,7] At present cure rates of 70% to 75% in localized forms of the disease are decreased dramatically in cases with poor prognostic factors at the onset: metastatic disease, in particular multiple or bilateral pulmonary lesions and secondary bone lesions, and axial localization of the disease, in particular the pelvis.[8–15]

There is consensus that the surgical approach is fundamental in the cure of osteosarcoma, and there have been only a few published cases of osteosarcoma patients treated and cured without surgery. Poppe et al reported in 1968 a case (details of the patient were not given) who survived more than 10 years after radiotherapy alone.[16] Beck et al in 1976 presented a case of osteosarcoma of the mandible (which is generally considered to have a better prognosis) that was treated with radiotherapy only, with a disease-free survival of more than 4 years.[17] Barwick et al in 1980 described a case of vertebral osteosarcoma in a 3-year-old boy treated with radiotherapy and chemotherapy: he died of multiple metastases after 6 years 2 months of survival.[18] Ogihara et al described in 1984 a patient with localized osteosarcoma of the fourth thoracic vertebra, with paraplegia, who was treated with four cycles of intra-arterial doxorubicin followed by chemotherapy according to COMPADRI-III regimen (cyclophosphamide, vincristine, methotrexate, phenylalanine mustard, and doxorubicin).[19] Surgical removal was not carried out as the lesion was inaccessible. Paraplegia regressed and the patient was disease-free with no neurologic deficit 6 years from diagnosis. Jaffe et al recently presented the results of their study that started in 1978 to evaluate the efficacy of chemotherapy alone to treat osteosarcoma.[20] The therapy did not include surgery as the first-line approach, but chemotherapy with high-dose methotrexate or intra-arterial cisplatin and maintenance chemotherapy including high-dose methotrexate, intra-arterial cisplatin, and doxorubicin. Thirty-one patients under 16 years with nonmetastatic osteosarcoma of the extremities were enrolled. Three initially obtained a clinical-radiologic response with high-dose methotrexate and 28 with intra-arterial cisplatin. However, at the last follow-up in September 2000, only three patients were alive without evidence of disease at 204 to 225 months from diagnosis. Four other patients achieved a complete response but asked to undergo surgical removal of the lesion: histologic examination of the resected specimens showed the absence of viable tumor. The authors concluded that chemotherapy alone rendered 10% of patients in the study disease-free. This percentage rose to 23% when the four disease-free patients who requested surgery were included. Jaffe et al underscored how obtaining good necrosis of the tumor, even 100%, did not mean the patient was cured, as a second relapse could not be ruled out, and that with 70% to 75% of patients cured by combined chemotherapy and surgery approaches, chemotherapy alone as the sole treatment of choice for osteosarcoma does not appear warranted.

The prognosis of our patient was extremely poor, considering the presence of multiple pulmonary and bone metastases and the fact that the primary site of the disease was inoperable. The diagnosis was the subject of much debate, but the histologic examination of highly undifferentiated high-grade malignant osteosarcoma was confirmed. Although it is an isolated case, it is worthy of note. In our opinion, removal of the primary and secondary lesions, when feasible, is essential in the treatment of osteosarcoma. Today, the possibility of carrying out an increasing number of limb-salvage operations and the evaluation of the tumor necrosis induced by preoperative chemotherapy are fundamental elements. On the other hand, generally the efficacy attributed to chemotherapy is thought to be temporary and regrowth of the tumor inevitable if surgical resection is not performed. The rapid and persistent clinical response observed in our patient, with a prolonged follow-up, may be considered an indication of the efficacy of aggressive chemotherapy in treating osteosarcoma.

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