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Metastasis of Osteosarcoma After 16 Years

Here we report the striking case of a 60-year-old patient who presented 16 years after the initial diagnosis of parosteal osteosarcoma of the humerus with a new extensive lung lesion. Using comparative genomic hybridization (CGH) and fluorescent in situ hybridization (FISH), we were able to confirm a late relapse of the initial osteosarcoma. More than that, we backtracked a 28-year long tumor evolution—a case report of an extraordinary clinical course and a review of the current literature including clinical implications.

A 60-year-old patient was admitted to our department. Lately, he had noticed shortness of breath on exertion, though otherwise in an excellent general condition. Feeling some kind of physical impairment he had consulted his primary physician who had referred him to our hospital.

The patient was quite familiar with our institution: Sixteen years ago he had been diagnosed with an osteosarcoma of the right humerus (Fig 1) after being under clinical observation for another 12 years. In 1981, there was retrospectively a first radiographic correlate of a parosteal tumor without any clinical manifestation at that time. In 1993, a resection had been followed by a polychemotherapy according to the Cooperative Osteosarcoma Study Group 86 protocol, leading to a complete remission and allowing the patient an active normal life.

On auscultation there was no audible breath in the left lung. A laboratory work-up showed a massively elevated lactate dehydrogenase (1,600 U/L), all the other parameters being within the normal limits. Our next diagnostic step was imaging of the chest. A computed tomography scan (Fig 2) revealed a massive tumor of the left lung.

A computed tomography–guided transthoracic biopsy was performed, but was unfortunately not diagnostic. A complete staging

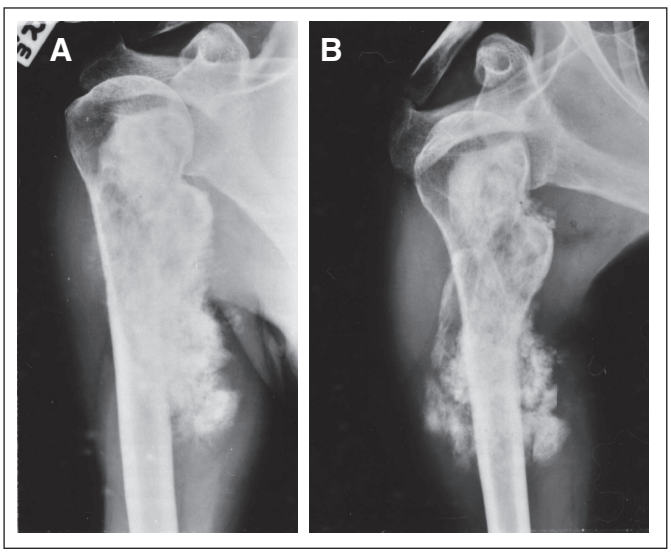

Fig 1.

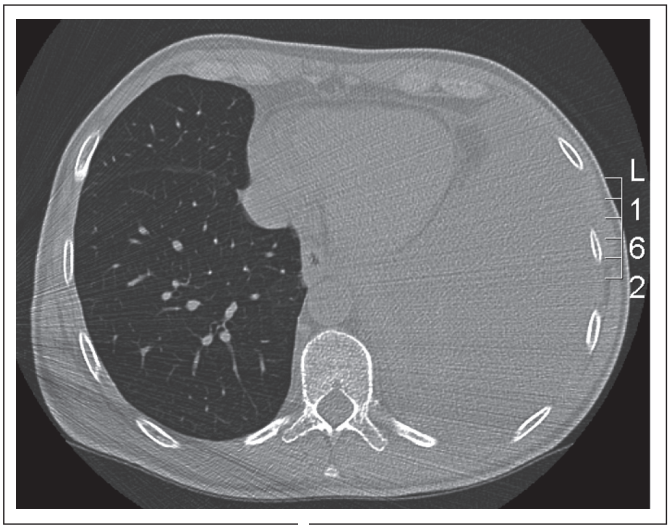

Fig 2.

showed no further tumor manifestation. The case was discussed in our interdisciplinary tumor board. The general recommendation was to aim for a resection if technically feasible. Regardless of the precise nature of this mass, surgery was most likely the only curative therapeutic approach. In addition, more material would help to come up with a final diagnosis.

A resection of the left lung including the C5 rib was performed without any major complications. The resected tumor measuring $20 \times 12 \times 11$ cm turned out to be an osteoblastic, partially chondroblastic differentiated osteosarcoma.

Comparison of archived material from the primary tumor aroused strong suspicion of a late relapse after 16 years. Histologic slides from the primary tumor revealed a similar histology (Fig 3A; arrows), even though the proliferation rate was higher in the lung metastasis as shown by a pronounced Ki-67 index (Fig 3B; arrows).

In 1993, the final diagnosis had been: dedifferentiated parosteal osteosarcoma with chondroblastic differentiation. Interestingly in 1981 the same patient had presented with retrospectively morphologically what was most likely the same tumor. This means that we can backtrack a 28-year-course of tumor evolution.

The paraffin embedded material from 1993 and 2009 was further analyzed by histo-morphological comparison, CGH and FISH. CGH revealed high copy amplification on the short arm of chromosome twelve in the primary sarcoma and metastasis. The CGH karyotype in 1993 was: ish cgh amp12q14; enhanced 12p11-p13.3. In contrast the CGH karyotype of the metastasis in 2009 was much more complex: ish cgh amp12q14; amp12p11-p13.3; amp8q24; enhanced 2q22-q23; 2p14; 4q31;14q12-q13;17p11-p13;17q22-q25;20q13;22q13;Xp11-p22; diminished 4p14-p16;5q14-q23;6q14-q21;10p14-p15;13q13-q31 (Figs 4A and 4B; examples of the reverse hybridization). FISH with a MDM2 specific probe—a potential candidate gene on chromosome

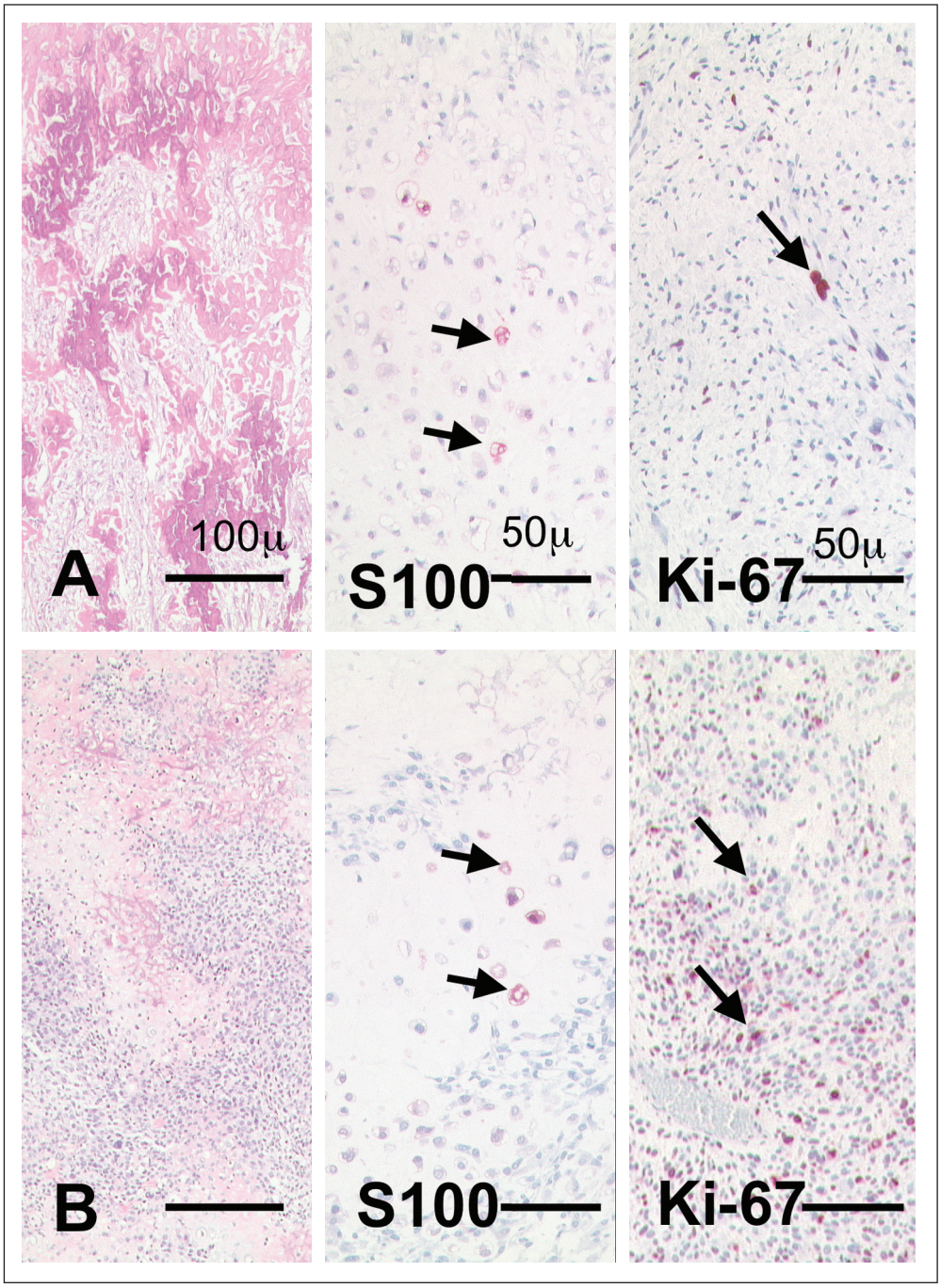

Fig 3.

12 to drive bone tumor development[1] and characteristic for parosteal subtype—showed a high level of DNA amplification of this region in both tumors (Fig 4C). This data lead to the conclusion that the MDM2 amplification was already present in the primary parosteal osteosarcoma. However, the clone surviving chemotherapy had gained further amplifications and deletions in comparison to the primary tumor. One could speculate that the observed genetic evolution is partly due to the selection pressure imposed by chemotherapy leading to a high aggressive metastasis.

The sarcoma cells are positive for MDM2 in the cytoplasm and in the nucleus suggesting a gene dosage effect (Fig 4D; bar = 100μ).

Our patient received two adjuvant courses of chemotherapy with carboplatine and etoposide and is currently treated with interferon alpha as consolidation.

To our knowledge, this is the case report with the longest time interval between adequate initial therapy including surgery and (neo)adjuvant chemotherapy and late metastasis in literature. There is also no report of pulmonal recurrence of comparable dimension.

In 0.6% to 5% of patients, first distant metastasis or local relapse occurs 5 years or more after initial treatment.[2,3] Revising literature, lung metastasis of osteosarcoma mostly appears early. Glasser et al[4] reported a median time of 11 months in a study including 279 patients.

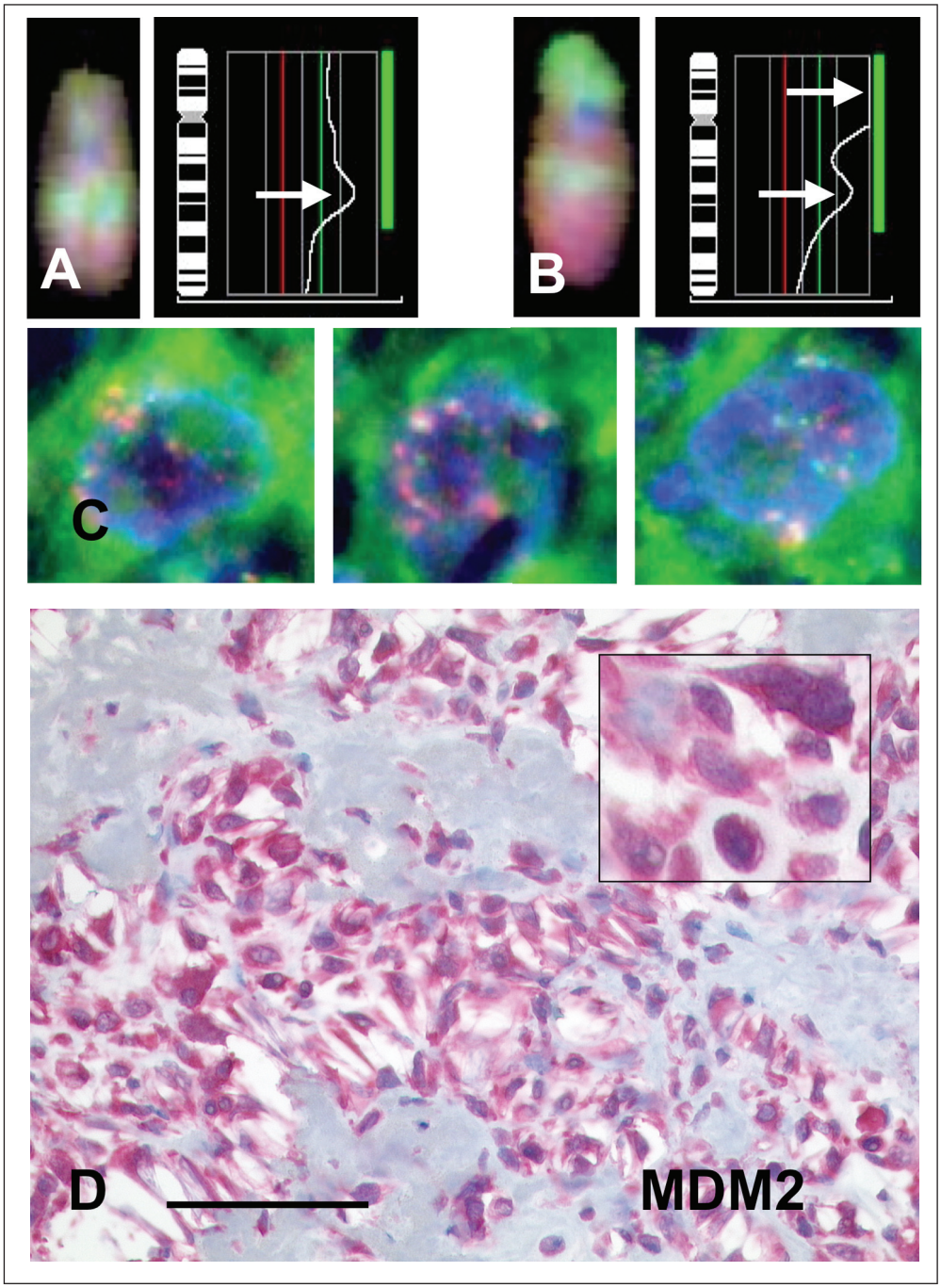

Fig 4.

Cooperative Osteosarcoma Study Group[5] reported a late recurrence in 23 of 1702 (1.4%) patients. The longest disease-free period was 14 years. Strauss et al[3] published the clinical course of eight patients treated in their institution developing late recurrence, three of them relapsing in the lung after 7, 8 and 14 years.

In 2004, there was a case report of local recurrence of a parosteal osteosarcoma adjacent to prosthesis after 20 years[6] pointing to a particular biology of this histological type. Primary location was distal femur and initial therapy consisted of wide excision and reconstruction with prosthesis, the patient did not receive chemotherapy. Looking closer at this report, time to recurrence is most likely shorter than reported: Three years after initial symptoms, diagnosis was histologically confirmed having initially been classified as fibrous dysplasia and therapy was performed after another 12 months. The interval from initial adequate surgery to recurrence is rather less than 16 years. Furthermore, it is likely that the proximity of the prosthesis complicated imaging and delayed proof of the relapse since symptoms started clearly earlier.

Welck et al[7] described a local recurrence of intramedullary osteosarcoma 17 years after initial diagnosis and state to report the longest

clinical course under comparable conditions. Maeda et al[8] reported a small lung metastasis 21 years after initial diagnosis of an osteosarcoma (without further specifying the histological subtype) of the femur leading to amputation. In contrast to our patient, their patient had refused adjuvant chemotherapy and had not received treatment including chemotherapy according to the state of art.

As a general consideration chemotherapy although greatly improving the long-term outcome may alter the natural behavior of osteosarcoma and delay time of relapse thus making late recurrence less rare.[3]

Hauben et al[2] performed a clinical study including 2,243 patients to further characterize possible predictive clinical and pathological features putting the patient at higher risk of late relapse (first recurrence 5 years or more after initial treatment). Only patients aged under 40 at time of diagnosis were included. Further inclusion criteria were primary, localized, high-grade central extremity osteosarcoma. A total of 3% had a late recurrence, 85% relapsed with metastasis, 12% locally and 3% had a combined recurrence. Assessing initial response in all patients that relapsed, late recurrence seemed to be more frequently in those with good initial response to chemotherapy. Gender or age seemed to have no predictive value. There was a trend for chondroblastic subtype to have a higher chance of late relapse. Location in tibia or fibula seemed to point versus predisposition - though not statistically significant. Summarizing the point of view of Hauben et al, the typical patient at high risk for late recurrence would be a person with chondroblastic osteosarcoma of the tibia with good initial chemotherapy response developing metastasis. Interestingly, our patient did have a chondroblastic differentiation but histologically did not respond well to initial chemotherapy.

Ferrari et al[9] looked at sex, site, tumor size, histologic subtype, alkaline phosphatase and lactate dehydrogenase serum levels, type of surgery and histologic response. As no predictive factor could be identified they recommend a prolonged follow-up for all patients. The difficulty as always when studying rare clinical conditions, is the number of patients per subgroup that gets small even though the total number included might be high, which complicates the detection of reliable prognostic markers.

The cause of delayed lung metastasis is poorly understood and is a matter of ongoing discussion. Tumor dormancy[10] or immune regulation[11] are current concepts.

Osteosarcoma is the most common primary bone tumor and lung is the most frequent metastatic site. Pulmonary metastasis has a major impact on the prognosis of those patients[12]; it occurs in approximately half of the patients and is the most common cause of death.[13] In general, patients are considered cured if they are disease-free for 5 years after therapy leading to a complete remission. Even though relapse 5 or more years after initial treatment of osteosarcoma is rare, these patients do exist. Clinical courses as reported, impose questions like: How late is late? Can we ever confirm they are cured? While clinical and molecular prognostic factors of osteosarcoma are studied,[14] there is so far only a vague idea about prognostic relevant factors for late recurrence.

More (clinical) studies with a large number of patients to predict possible clinical and histopathologic factors are certainly mandatory. How should we proceed in this vague situation? Is longer follow-up required for patients at risk? Is currently available data sufficient to define patients at higher risk for late relapse? Or would we rather waste time and money in the age of economization?

Strauss et al[3] made the statement in 2004 that it is essential to continue regular follow-up of patients beyond 5 years. Hauben et al[2] in 2006 stressed their findings by recommending longer follow-up in patients with chondroblastic subtypes, primary location in tibia and fibula and good initial response to chemotherapy. Maeda et al[8] extend this and demand to follow patients with a past history of osteosarcoma for their entire life.

At present it is challenging to come up with general guidance. What is certainly warranted is to stay alert when patients are presenting even with mild symptoms after many years and keep metastases in mind when lung nodules or tumors are investigated. Promising approaches for future risk stratification might be molecular-based methods such as gene expression profiling. There are ongoing efforts to establish methods that aim for assessments of survival times and prognostic indices in human beings.[15,16] However the good news is that even though there is data (albeit limited) pointing towards a poor prognosis of late recurrence[3] our patient remains in complete remission 7 months after treatment of his relapse.

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