

Histiocytic lymphadenopathy secondary to metallosis following endoprosthetic replacement in osteosarcoma patient – a potential diagnostic pitfall

Kamil Sokół^{1,2}, Bartłomiej Szostakowski³, Maria Chraszczewska^{1,2}, Tomasz Goryń³, Michał Wągradzki¹, Monika Prochorec-Sobieszek^{1,2}, Anna Szumera-Ciećkiewicz^{1,2}

¹Department of Pathology and Laboratory Diagnostics, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

²Department of Diagnostic Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

³Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

We present the case of a 43-year old patient with inguinal lymphadenopathy 22 years after distal femoral resection for osteosarcoma with cemented distal femoral replacement reconstruction. Seven years after initial distal femoral resection patient underwent metal on metal hip resurfacing arthroplasty on the affected side. Twenty years after distal femoral replacement and 13 years after metal on metal hip resurfacing procedure, the patient underwent left inguinal lymphadenectomy for an enlarged mass of inguinal lymph nodes on suspicion for a sarcoma recurrence. On microscopic examination, excised lymph nodes were massively infiltrated with macrophages and multinucleated giant cells with focal asteroid bodies. An examination in polarized light revealed numerous metal particles; immunohistochemical stainings confirmed reactive character of changes, and florid metal-related sinus histiocytosis was finally diagnosed. Microscopic assessment of lymph nodes in the course of malignancy is a standard procedure; we present a rare case of non-neoplastic lymph node enlargement due to the late onset of metallosis, which might be a diagnostic challenge.

Key words: metallosis, osteosarcoma, lymphadenopathy, endoprosthesis, metal on metal

Introduction

Lymphadenopathy in patients who underwent osteosarcoma treatment firstly suggests metastatic spread, however other potential causes must also be considered as lymph nodes are parts of an immune system which functions include filtration of various antigens from the extracellular fluid. Lymph nodes consist of macrophages, lymphocytes, and antigen-presenting cells, depending on the immunological status, age, and localization [1]. Essential differential diagnosis of enlarged lymph nodes leads to classification into one of a category: infectious (fungal, viral, protozoal, bacterial), inflammatory (drug, foreign body), neoplastic (primary neoplasm, metas-

tasis), trauma, autoimmune, idiopathic (e.g., sarcoidosis). Often hematoxylin and eosin staining can target differential diagnostics; usually, additional immunohistochemical and/or histochemical evaluation is necessary. The critical point to the exclusion of sarcoma metastasis or primary lymph node malignancy (lymphoma) is morphology. In the histopathological assessment of osteosarcoma, no specific antibodies are routinely used, and in the absence of data from the medical history or a non-specific microscopic appearance, a broad immunohistochemical panel is used to narrow down the diagnosis. In the presence of foreign particles, it is suggested to perform the microscopic evaluation in polarized

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light; some metal particles, including steel alloys, may exhibit birefringence with pale green luminescence [2, 3].

In our paper, we present a case of histiocytic lymphadenopathy secondary to metallosis following limb-sparing surgery for osteosarcoma and metal on metal hip resurfacing on the affected side. The differential diagnosis with a discussion of overlapping morphological images are revised.

Material and methods

Clinical history

A 43-year-old Caucasian male was admitted to the hospital due to enlarging left inguinal mass. In 1998 patient underwent limb-sparing resection and reconstruction of the distal femur for a classical high-grade osteosarcoma (fig. 1: A, B). The patient was initially fitted with a cemented distal femoral replacement in 1998, followed by metal on metal hip resurfacing in 2005 for hip arthritis (fig.1: C, D). The patient had a soft tissue relapse of osteosarcoma in 2002 that was treated with a second-line chemotherapy and radical excision. Due to previous oncological history, the enlarged inguinal mass was suspected to be a metastatic relapse of osteosarcoma. Ultrasound examination showed enlarged lymph nodes – the largest measuring 28 mm in diameter. Radiologist described lymph nodes as suspicious for a neoplastic process. Fine needle biopsy of the lymph node showed only elements of a peripheral blood smear. There were no significant changes in laboratory tests. Lymph nodes were surgically removed and examined histopathologically.

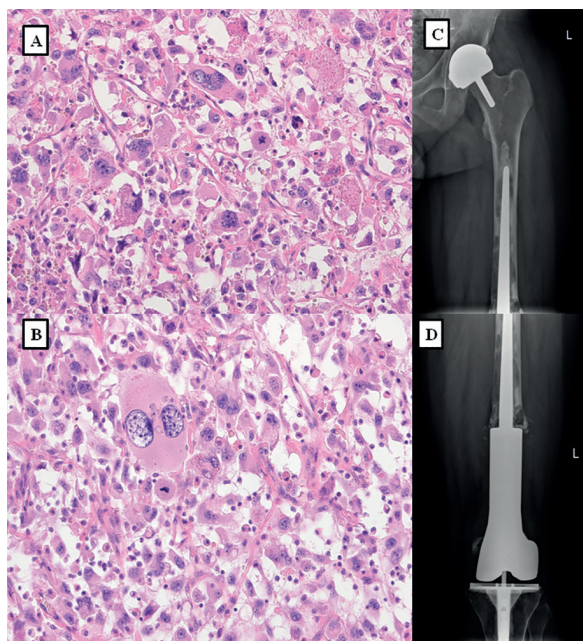


Figure 1. A, B – microscopic presentation of primary bone osteosarcoma, highly apoptotic with scattered “giant” neoplastic cells (A – HE, 200x; B – HE, 400x); C, D – X-ray showing cemented distal femoral replacement and metal on metal hip resurfacing in 2013 and in 2018 when the progression of a stem loosening and cortical thinning is clearly visible

Histopathology

The resected lymph nodes were fixated with 4% formalin and paraffin-embedded; the five μm -thick sections were made for hematoxylin and eosin staining (HE), Grocott-Gomori’s methenamine silver (GMS), Periodic acid–Schiff (PAS), acid-fast stain (AFB), and immunostained with S100 (RTU, DAKO-Agilent), CD23 (RTU, DAK-23, DAKO-Agilent), CD20 (RTU, L26, DAKO-Agilent), Ki-67 (RTU, MIB-1, DAKO-Agilent), CD68 (RTU, KP1, DAKO-Agilent), CD163 (RTU, MRQ-26, Cell Marque), CD1a (RTU, 010, DAKO-Agilent), CD3 (1:50, F7.2.38, DAKO-Agilent).

Results

Histopathological and immunohistochemical findings and visualization in polarized light

Microscopically, a reactive lymph node with massive histiocytic and macrophage infiltration. There were many giant multinucleated cells, some with asteroid bodies. Macrophages showed a lot of “dust” particles that were bright green in the polarized light. The histochemical stains (PAS, GMS, AFB) did not indicate any microorganisms; CD3 showed normal mantle distribution of small T-cells, CD20 pointed germinal center B-cells, CD23 revealed a typical structure of dendritic cells in the germinal center, there were few Langerhans cells CD1a-positive. Macrophage infiltration was CD68KP1 and CD163-positive. Ki-67 was high in germinal centers; it was low, below 5% elsewhere. Finally, the diagnosis of florid metal-related sinus histiocytosis was made. The histopathological, immunohistochemical, and polarized light images are presented in figure 2.

Discussion

Bone malignant neoplasms are relatively rare and consist of only 0.2% of incidents of malignancies in Poland [4]. There are twice as frequent in men as in women. The most common bone sarcoma is osteosarcoma, with 60–100 new incidents per year. Osteosarcoma has a bimodal age distribution, having the first peak during adolescence and the second peak in older adulthood [5]. Osteosarcoma develops most often at the metaphysis of lower extremity long bones (~75% of cases). Histologically osteosarcoma demonstrates malignant spindle cells with pleomorphic nuclei, scattered mitotic figures, and varying levels of anaplasia. Conventional osteosarcomas are classified into osteoblastic, chondroblastic, or fibroblastic types, depending on which matrix-producing cells dominate [6–8].

Before the development of chemotherapy, osteosarcoma was a fatal disease with severe outcomes. Patients with locally advanced tumors used to develop metastases in the lungs and bone marrow quickly and died a few months after [9]. Less common histological subtypes like osteoblastoma-like and chondroblastoma-like osteosarcoma more common metastasize than its’ conventional counterparts [10]. Metastases of osteosarcoma in lymph nodes are rare entities; most reports estimate that it occurs in about 1–4% of patients with

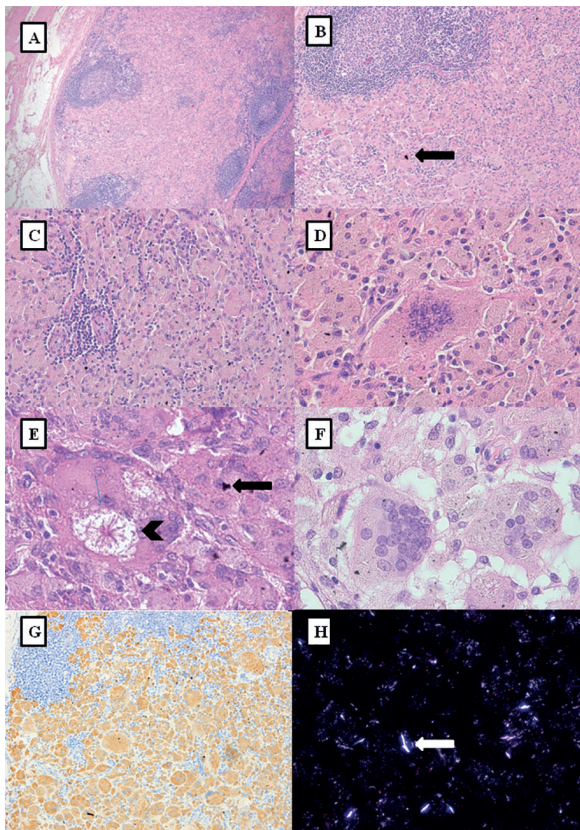


Figure 2. Metal-related sinus histiocytosis. **A, B, C** – lymph node with massive histiocytic and macrophage infiltration, with sparse typical germinal centers preserved (A – HE, 20x, B – 100x, C – 200x); **D, E, F** – giant multinucleated Langhans cells, some with asteroid bodies (arrowhead) and macrophages with black metal "dust" (arrow) which were released from endoprosthesis (D – HE, 400x, E – HE, 1000x, F – HE, 600x); **G** – CD63 diffuse positive reaction among macrophages (CD163, 200x); **H** – macrophages are presenting with the "dust" bright particles in the polarized light (HE, polarized light, 400x)

osteosarcoma [11, 12]. We found no literature describing any connection between the histological type of osteosarcoma and lymph node metastases rate. Adjuvant chemotherapy and surgery procedures highly improve outcomes [10, 13]. Development of modern endoprosthetic reconstruction techniques and the introduction of modular tumor endoprostheses heavily reduced the number of amputations in osteosarcoma patients [9, 14, 15].

Endoprostheses of joints can wear in time, producing debris particles in surrounding tissues [16–18]. The generation of wear debris from any part of the prosthesis is unavoidable. Implant loosening secondary to osteolysis is the most common mode of failure of arthroplasty [19]. Local and regional lymphadenopathy that is caused by wear particles released from a joint-replacement prosthesis is increasingly becoming recognized as a possible complication of arthroplasty [20]. Accumulation of such particles causes an inflammatory response, including macrophagic activation with the formation of giant cells and fibrosis. Soft tissue infiltration by metal debris shed by the prosthesis or lymphatic uptake of metal debris following its wear is called metallosis [17, 21].

Local lymphadenopathy in patients with endoprosthetic reconstruction needs differential diagnosis of joint infection, implant-associated allergic reaction, or hypersensitivity related to implant itself. In some cases, those particles from prosthesis are drained through lymph vessels to regional lymph nodes [3, 22]. Accumulation of histiocytes with the debris is responsible for the enlarging of lymph nodes – some histiocytes fuse in multinucleated giant cells [20]. Metallic particles are usually seen as very small (0,5–5 μm) dark brown or black bodies. Other components of a prosthesis (usually polyethylene, polymethyl-methacrylate) are bright and not seen in HE staining in a light microscope, but are bright in polarized light [23].

It has to be emphasized that only some of the patients after joint replacement surgery develop lymphadenopathy [3]. Different studies describe that the metallosis rate depends on materials and operated joint and happened in about 5–23% of patients [17, 21]. It seems that there is no explanation for this phenomenon. In animal models, 1% of radioactive label particles injected intra-articular sites migrated to regional lymph nodes after 24. In a similar experiment, radioactive label particles were injected into femur bone marrow. In that case, particles moved to the lung via the blood vessels within 15 seconds, and no migration to the lymph node was detected [20].

Histologically, asteroid body is characteristic but not specific microscopical finding. Although it is commonly associating with sarcoidosis [24] and may occur in different pathological diagnoses. e.g. foreign body reaction in silicon transplant leaking [25, 26], other foreign body reaction [27], fungal infection [28], rarely in some neoplasm [29]. As in our case, palpably asteroid body mechanism of creation is similar for that in foreign body reactions [30, 31].

Besides local symptoms, the presence of metal and ethylene particles in a human body may also cause generalizes symptoms like cardiomyopathy, neuropathy, psychological status changes, skin rash, visual impairment [17]. It is essential to recognize this state and introduce treatment before generalized symptoms occurred. Treatment includes surgical revision of prosthesis, removal of damaged parts, and changed tissues and bone grafting [17, 21].

Conclusion

Enlarged lymph nodes in tumor surgery patients may be suggestive of a recurrence of the malignancy; however, both neoplastic and non-neoplastic conditions must also be considered. We presented a case of a lymph node foreign body reaction in the form of florid histiocytosis in osteosarcoma patient after long-term follow up of both limb-sparing surgery with massive endoprosthetic reconstruction and metal on metal hip resurfacing. It is important to know that both implants are prone to massive wear debris, especially after long term follow up, resulting in catastrophic failures [32, 33]. Histiocytic lymphadenopathy secondary to metallosis in patients who underwent joint replacement surgery is usually indicative

of increased endoprosthetic wear that requires immediate attention, usually followed by revision surgery. It is paramount to compare both clinical and radiological presentation for a complete image.

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Conflict of interest: none declared

Anna Szumera-Ciećkiewicz

*Maria Skłodowska-Curie National Research Institute of Oncology
Department of Pathology and Laboratory Diagnostics
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: szumann@gmail.com*

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