Secondary osteosarcoma arising on one of multiple areas of avascular bone necrosis caused by corticosteroid therapy: case report and review of the literature

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Case report

A 66-year-old male was referred to our hospital with a three-months history of pain and increasing swelling on the left thigh and knee, without prior trauma.

Forty-two years before, this patient received a diagnosis of idiopathic medullary aplasia, for which he received steroid therapy, with subsequent development of multiple areas of bone necrosis. After 28 transfusions, hematologists performed a therapy with anti-lymphocytic globulin and high-dose bolus methylprednisolone, ultimately leading to the complete resolution of bone marrow disease.

The patient arrived at our hospital for the presence of pain and swelling on the left thigh, a bilateral MRI and computerized tomography CT-scan of the knee were performed, revealing typical map lesions of bone necrosis in both distal femurs and proximal tibias. Additionally, in the left thigh, a mass adjacent to the necrosis with destruction of anterior and posterior cortices and subsequent leakage of heteroplastic tissue out of the bone was evident.

Orthopedics, elsewhere, also performed incisional biopsy of the mass, with a histological diagnosis of pleomorphic sarcoma. No parenchymal lesions were evident upon CT-scan of the chest. Total-body PET showed uptake on distal left femur (SUV 31). The patient started neoadjuvant chemotherapy with Epirubicin and Ifosfamide.

Laboratory exams before surgery showed normal RCP (0,25 on 0,5) and LDH (225 on 248) levels, as well as increased VES (39 on 20) and ALP (263 on 120). The patient had mild pancytopenia due to chemotherapy.

The patient was treated with three courses of pre-operative chemotherapy: at the end of the second course, he had pathological fracture making a movement lying in bed. A knee brace locked in extension has been placed during the last chemotherapy course; meanwhile he developed external sciatic popliteal nerve palsy. Limb salvage surgery with distal femur resection and mega-prosthesis was performed at the end of preoperative chemotherapy.

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Histological examination of the specimen revealed a lesion measuring 14x6x6cm, that histologically corresponded to extensively necrotic high-grade osteoblastic OS, (95% of necrosis, grade 3 according to Huvos) [8]. Surgical margins were wide.

After 6 months, periprosthetic joint (PJI) infection occurred; firstly, it was treated with irrigation and debridement, nonspecific antibiotics (intraoperative cultural exams not performed) and VAC-therapy. This approach was not successful, RCP was always out of range, sinus still present, thigh and knee warm and painful, so, two months later, he underwent explant of the prosthesis and vancomycin-added cement spacer. Intraoperative histological examination showed chronic and acute inflammation, Pseudomonas Aeruginosa was detected in all intraoperative cultural exams; therefore, specific oral antibiotic therapy was administered.

Every twenty days, the patient performed laboratory blood exams for RCP and VES, in order to check the inflammatory status. RCP and VES were normal in every examination, so, after sixty-nine days after for RPC and VES, in order to check the inflammatory status. RCP and VAC-therapy. This was administered.

X-ray films of left thigh and knee at 40 days after last surgery showed no mechanical complications. At the last follow up, 12 months after first surgery, there was no evidence of local recurrence or metastases.

Discussion

Secondary bone infarct-related OSs represent about 1% of all osteosarcomas [7]. In most cases, bone infarcts are occasional findings on X-ray films, since they are asymptomatic lesions. Their exact etiology is unknown. They can be idiopathic, or related to prior trauma, alcoholism, hematologic disorders such as sickle cells disease, and chronic use of steroids. Torres and Kyriakos in 1992 described 4 patients with OS on bone infarct in multiple areas of bone avascular necrosis, but they did not specify any information about the etiopathology of the multiple bone infarcts [3].

Here we reported a case in which the origin of bone infarct is known and documented.

Different types of sarcomas are able to grow on top of a bone infarct, with the most common being undifferentiated pleomorphic sarcoma (UPS) at 63%, followed by OS at 18% and fibrosarcoma (FS) at (13,2%) [1].

Secondary bone infarct-related OS generally affects the older-aged population more frequently than conventional osteosarcoma [1]. In the literature, the mean age is 57-year-old; two-thirds of patients are male [6]. The time interval between bone infarct and sarcoma development is unknown, as the infarct is asymptomatic. Torres et al. [3] found that the time interval from last exposure to compressed air conditions, thought to be the timing and cause of bone infarct, was many years, in some cases more than 20. A slow and steady reparative stimulus on infarct area, could achieve the growth of OS above it as final result, which is coherent with the idea that secondary OS affects populations of older ages compared to those with primary OSs.

Bone infarct-related OSs most frequently arise in the distal femur, proximal tibia, and proximal femur, while they are rarely seen in the humerus [7].

Most patients presented with pain and swelling in the area of bone infarct, sometimes with pathological fracture.
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Table 1. Literature series of OS on bone infarct

| Case | Age | Sex | Site          | Treatment          | Course                      |
|------|-----|-----|---------------|--------------------|-----------------------------|
| 1    | 48  | M   | Proximal Tibia| XRT, Amputation    | Lung METs at 3 month; Died at 9 mo. |
| 2    | 61  | M   | Distal Femur  | XRT, Amputation    | Lung METs at 1 month; Died at 3 mo. |
| 3    | 79  | M   | Proximal Femur| Resection          | Died with lung METs at 19 mo. |
| 4    | 56  | F   | Proximal Femur| Amputation         | Lung METs treated with Chemotherapy; Died at 40 mo. |
| 5    | 35  | M   | Proximal Femur| Amputation, Adjuvant CHT | Bone MET at 6 years treated with amputation; Alive at 57 months |
| 6    | 61  | F   | Proximal Tibia| Amputation         | Chest and spinal canal METs at 12 mo.; Died few weeks after|
| 7    | 82  | M   | Proximal Humours| Amputation      | Died with lung METs at 12 mo. |
| 8    | 56  | M   | Proximal Tibia| Resection         | Not Reported                 |
| 9    | 35  | F   | Distal        | Amputation         | Dead at 24 mo.               |
| 10   | 55  | M   | Proximal Tibia| Neo-adjuvant CHT, Amputation| Alive at 58 mo.               |
| 11   | 75  | F   | Distal Femur  | Resection         | Died at 5 mo.                |
| 12   | 35  | M   | Proximal Femur| Palliative XRT     | Lost to follow-up less than 1 mo. after |
| 13   | 61  | M   | Distal Femur  | Amputation         | Dead at 11 mo.               |
| 14   | 36  | F   | Proximal Numerus| Resection      | Alive at 4 years.            |
| 15   | 72  | M   | Proximal Numerus| Neo-adjuvant CHT, Amputation| Died at 7 mo.               |

XRT = radiotherapy; CHT = chemotherapy; MET/METs = metastasis/metastases; mo. = months

Table 2. Overall Survival estimates at different time point of follow up

| Time      | Outcome | Literature cohort | [95% Conf. Int.] |
|-----------|---------|-------------------|------------------|
| 12-OS     | 0.54    |                   | 25-76            |
| 36-OS     | 0.36    |                   | Dec-61           |
| Median survival time | 19 months |                 | 7-not reached    |

3 months respectively. One patient underwent only radiotherapy and after two weeks he got lost to follow-up. Three, underwent surgery (amputation) as well as chemotherapy, two in the preoperative period, one postoperatively. Two of them were alive without evidence of disease at fifty-eight and fifty-seven months after surgery respectively, while one died of the disease at seven months (Figure 1-3).

Complete follow-up data are available for 12 patients, nine of them died of the disease (75%) Overall survival at 36 months was 36% (95% CI 25-76). Three patients survived without disease, two of them were those who underwent not only surgery, but more importantly chemotherapy in association, one preoperatively, the last postoperatively.

The patient presented in this report, has been treated with three standard preoperative chemotherapy courses, followed by surgical resection and megaprosthesis. He got into early PJI and resolution was obtained with surgical debridement, removal of the prosthesis and antibiotic-added cement spacer. At the normalization of inflammatory blood index, the spacer was removed, and silver-coated prosthesis was placed. After the last follow up, 12 months after distal femur resection, the patient was alive with no evidence of local recurrence neither distant metastases. Up to now, follow up examinations were performed every 3 months with X-ray film of left thigh and knee and CT-scan without contrast of the chest.

Conclusions

Patients with secondary bone infarct-related OSs have the best chances of survival with chemotherapy, combined with surgery. When possible neo-adjuvant chemotherapy, by shrinking tumour dimensions, limb salvage surgery became more possible rather than amputation. However, regardless of the type of local treatment, poor prognosis is related to development of lung metastases after surgery, and this confirms the key role of chemotherapy courses to deal with the treatment of this systemic disease.

Figure 1. MRI showed multiple bilateral bone infarcts around right and left knee, on the left distal femur necrotic area, heteroplastic tissue grown with rupture of cortices and soft tissue expansion

Figure 2. Pathological fracture of left distal femur and postoperative X-ray film of megaprosthesis reconstruction
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