Clear-Cell Chondrosarcoma

—A Case Report Suggesting a Malignant Variation of Chondroblastoma—

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Summary: We report a case of clear-cell chondrosarcoma at the upper end of femur of a 56 year-old woman. The tumor was first located eccentrically in the proximal epiphysis and had expanded even into the intertrochanteric region during the following three years. She developed spinal metastasis and died of pulmonary metastases ten years after the onset of the disease. Histologically, the tumor cells were found to exhibit the characteristics of both immature and mature cartilage cells. A close correlation between clear-cell chondrosarcoma and chondroblastoma was suggested not only by their locations but also by the close resemblance of the characteristics of their main tumor cells.

Key words: clear-cell chondrosarcoma — malignant chondroblastoma — bone — tumor — collagen — cartilage —

Introduction

In 1976, Unni et al. gave the name "clear-cell chondrosarcoma" to a group of cartilagenous tumors that originated in epiphysis and appeared histologically to be a distinct entity. The tumor is microscopically distinguished from a conventional chondrosarcoma by the main tumor cell, which has a central vesicular nucleus with strikingly clear cytoplasm and well defined cytoplasmic border, multinucleated giant cells not usually seen in conventional chondrosarcomata, and irregularly distributed lines of calcification. Although this tumor is now a definite entity, it is not yet known whether it is a variant of chondrosarcoma or a malignant variation of chondroblastoma. We report a case of the

tumor which supports the view that the tumor is a malignant variation of chondroblastoma.

Material and Methods

Case

A 56-year-old woman began to have pain in her left hip joint in 1973, when she was aged 52 years. In September 1975, she became unable to walk after a fall. Her physician performed an osteosynthesis with multiple pinning with a diagnosis of femoral neck fracture. No tumorous lesion of the femoral head was noticed. X-ray examination had then showed a well-demarcated, round radiolucency involving the medial aspect of the epiphysis

Fig. 1. Roentgenogram showing an osteolytic lesion in the upper end of the left femur with a pathological fracture through the neck.

Fig. 2. Roentgenogram one year after surgery showing osteosynthesis of femoral neck fracture with enlargement of the lesion.

Fig. 3. Photomicrograph showing typical clear-cell area. Tumor cells have a central vesicular nucleus with clear cytoplasm and well defined cytoplasmic border. Osteoclast-like giant cells and chondro-osteoid with deposits of calcium are also seen. (Hematoxylin-eosin, $\times 100$).

Fig. 4. Area of pleomorphic cells with acidophilic cytoplasm and eccentrically placed nucleus. (Hematoxylin-eosin, $\times 300$).

Fig. 5. Electronmicrograph showing various types of collagen. Type I collagen with cross-striations of 64 nm periodicity is dominant. Very fine type II collagen which is not cross-striated apparently showing extensive branching is identified. Long-spacing collagen is also seen. ($\times 36,000$)

of the left femoral head (Fig. 1). She did well for about one year, until she again became unable to walk after a fall in November 1976. X-ray examination revealed a pathological fracture located at the subtrochanteric region of the left femur. In December 1976, she was first seen at Kurume University Hospital. Roentgenograms of the hip revealed an expanding lesion to the neck and intertrochanteric region of the left femur (Fig. 2). Laboratory data were within normal limits, except for a slight elevation of alkaline phosphatase. With the diagnosis of chondrosarcoma, she underwent an operation of hemipelvectomy on 20 th January, 1977. In March 1978, she was discharged from this hospital. In May 1979, she began complaining of lumbago and abdominal pain. The pain progressively increased and she was admitted again in June 1979, with monoplegia of the right lower extremity. Roentgenograms showed a pathological compression fracture of the ninth thoracic vertebral body. On 4 th September, 1979, curettage and laminectomy with spondylosis was carried out. However, the neurological deficit did not recover. She died of pulmonary metastases on 21 st May, 1983. No autopsy was performed. The total duration of her disease from onset to death was 10 years.

Histology

The materials obtained in 1977 and in 1979 were histologically identical. Under low magnification, the lesions were lobular and showed various histological patterns. The principal tumor cells were distinctly outlined, and had a centrally placed, dark nucleus surrounded by clear cytoplasm. The nuclei were generally uniform, but some were larger and hyperchromatic. Mitotic figures were rare. The tumor was rich in capillaries with ground substance randomly laid down in a lattice-like pattern. Some of them showed a calcareous deposition. Osteoclast-like giant cells were

interspersed between the tumor cells and around the lines of calcification. These figures closely resembled those of chondroblastoma (Fig. 3). Areas of conventional low-grade chondrosarcoma were also recognised. These formed small inconspicuous foci among the clear cells. Pleomorphic cartilage cells with acidophilic cytoplasm and an eccentrically-placed nucleus were also seen. In this area, many mitotic figures were seen (Fig. 4). Tumor thrombi in the vessels were found in some sections of the specimen obtained from the vertebral lesion.

It was revealed that the matrix contained mainly chondroitin sulphate and additionally, hyaluronic acid and keratan sulphate by histochemical examination, which involved use of the Critical Electrolyte Concentration (CEC) method as introduced by Scott (1965), and alcian blue staining at different values of pH with and without pretreatment with bovine testicular hyaluronidase. Proteoglycans were less well identified in the clear-cell area than in the area of well-differentiated chondrosarcoma.

Ultrastructurally, the tumor cells exhibited a cartilagenous character containing a fair amount of glycogen, well-developed rough endoplasmic reticulum, and cytoplasmic process. In the extracellular matrix, proteoglycan granules and collagen of both Type I and II were identified (Fig. 5).

Discussion

The type of tumor designated as "clear-cell chondrosarcoma" was so named by Unni et al. in 1976, and since that time sporadic cases have been reported. However, controversy still exists as to whether the tumor is a variant of chondrosarcoma (Unni et al., 1976; Le Charpentier et al., 1979; Spjut et al., 1981) or a malignant variation of chondroblastoma (Schajowicz

Fig. 6. Photomicrograph of the case of chondroblastoma from our file showing a clear-cell pattern. (Hematoxylin-eosin, left; $\times 100$ right; $\times 200$).

1981).

The arguments in support of the former view include the following; firstly, the occurrence of malignant counterparts or malignant transformation of chondroblastoma has been denied (Jaffe et al., 1942; Dahlin, 1978), and secondly, the cells of chondroblastoma have a slightly acidophylic cytoplasm, whereas the dominant cell in clear-cell chondrosarcoma has a colourless cytoplasm (Unni et al., 1976; Spjut et al., 1981). However, cases have been increasingly reported such as of aggressive chondroblastoma (Coleman, 1966; Kahn et al., 1969; McLaughlin et al., 1975; Green et al., 1978; Wirman et al., 1979) and malignant transformed chondroblastoma (Sirsat et al., 1970). Chondroblastoma is not, therefore, considered to be so benign as had been hitherto believed. It is also well-known that some tumors may occasionally present a clear-cell pattern and, therefore, it seems difficult to differentiate clear-cell

chondrosarcoma from chondroblastoma only by the difference in the staining property of the cytoplasm.

We agree with the view that clear-cell chondrosarcoma is a malignant variation of chondroblastoma. The evidence in support of this is that the tumor was circumscribed within the epiphysis like chondroblastoma at first presentation, and in the following three years, the tumor revealed a malignant development, expanding into the metaphysis and destroying the cortex. Furthermore, the multinucleated giant cells, which are rarely seen in chondrosarcoma, were abundantly scattered throughout all the histological sections. This finding is a clear characteristic of chondroblastoma. Some cases of benign chondroblastoma, to our knowledge, demonstrate histologically, in part, a clear-cell change. These cells have a clear cytoplasm and a centrally located nucleus (Fig. 6). This closely resembles characteristics

of clear-cell chondrosarcoma. This also supports our view.

In the character of tumor cells there is no apparent difference between chondroblastoma and clear-cell chondrosarcoma. Our case was histologically composed of cartilage cells in the various stages of differentiation comprising areas of clear-cells, hyaline cartilage cells, and pleomorphic cells. Ultrastructurally, well-developed rough endoplasmic reticulum, glycogen, and collagen of both Type I and Type II were identified. As to collagen, only the mature cartilage cells are said to be able to produce Type II collagen though other precartilagenous mesenchymal cells produce the more ubiquitous Type I collagen (von der Mark et al., 1976; Dessau et al., 1980). Thus, the cells of our present case are considered to have the characteristics of both immature and mature cartilage cells. On the other hand, Levine (1972) has confirmed by an electron microscopic examination of chondroblastoma that the tumor cells have exhibited the characteristics of both immature and mature cartilage cells. He stated, then, that the term "chondroblastoma" might be a misnomer because the difference between differentiated neoplastic cells and truly embryonic cells had been taken into account in the naming of this neoplasm. The resemblance in the cell composition between the two neoplasms may also indicate a close relationship.

We also propose acceptance of the clear-cells and calcification coexisting in this tumor. Extracellular proteoglycans were less well identified in the clear-cell area than in the area of well-differentiated chondrosarcoma. Since proteoglycans are considered to prevent calcification, the decrease in proteoglycans in the matrix is, therefore, considered to provide available space required for the mineral to be embedded amongst the collagen fibrils (Howell, 1971). The mechanism of calcification in the epiphyseal plate is said to

be divided into two phases (Ali, 1983). In the first phase, the matrix vesicles are produced from a chondrocyte process in the lower proliferative zone and they there acquire calcium and phosphate ions for apatite formation by hydrolysis. In the second phase, the crystals grow in the matrix vesicles, then extend outward sufficiently to break through the vesicle membrane. In this phase mitochondria come also into play. Mitochondria of chondrocytes accumulate calcium in the upper hypertrophic zone then appear to transfer the calcium into the extracellular matrix in the lower hypertrophic zone. The cells in the clear-cell area may, therefore, correspond to proliferative and/or hypertrophic cartilage cells.

In summary, therefore, our case suggests the probability of clear-cell chondrosarcoma being a malignant variation of chondroblastoma. This is important because it implies that chondroblastoma is not always "benign" as Jaffe and Lichtenstein (1942) had postulated. The tumor must be surgically resected to prevent recurrence, since any recurrence would increase the possibility of a malignant development.

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