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Pre-Sacral Chordomas, about Two Cases and Review of the Literature

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Abstract

The World Health Organization (WHO) defines chordoma as a malignant tumor of intermediate or low grade, developing at the expense of embryonic remnants of the notochord. These tumors represent 8.4% of all malignant bone tumors. We report 2 cases collected in the medical oncology department at the CHU Hassan II in Fes. In whom the clinical examination revealed a mass and/or signs of loco-regional compression. The tumor was located in the sacrum in both patients. The diagnosis was based on the data of the anatomopathological examination showing the association of a lobulated architecture with classic physaliphore cells and a mucoid intercellular substance. Immunohistochemistry was performed for both patients. The principle of therapeutic management was based on radiotherapy and targeted therapy since surgery was difficult given the local tumor extension.

Keywords

Chordomas, Imatinib, Radiotherapy

1. Introduction

Chordoma (CH) is a rare malignant tumor which represents 8.4% of all primary malignant bone tumors developing from the remnants of the notochord essentially at the expense of the axial skeleton. It mainly affects adults. Because of its rarity, it often poses a double problem, of diagnosis and therapeutic management. Advances in this field have been made thanks to immunohistochemistry and new radiotherapy techniques. We report the experience of the medical oncology department at the CHU Hassan II of Fes, in the management of these tumors through 2 cases collected in our institution and we discuss the clinical and anatomopathological characteristics of this entity as well as the difficulties of

taking in therapeutic management based on data from the literature published on this subject.

2. Cases Presentation

2.1. Case 1

This is a 21-year-old single patient with no significant pathological history.

The history of his pathology began with the appearance of spontaneous pain next to the sacral region at great intensity hampering the sitting position, the symptomatology then worsened with the appearance of constipation as well as bloating while evolving in a context of conservation of the general state which motivated its consultation for support.

Physical examination:

PS patient at 0

large mass in left hypochondrium, painless, mobile with respiration

rigid hypogastric mass

clinically free inguinal and supraclavicular lymph node areas

Initial radiological exploration by:

CT scan of the lumbar spine:

Bulky pre-sacral formation with opposite vertebral sacrocoxygeal osteolysis suggesting primarily a pre-sacral chordoma, but without eliminating a solitary neurofibroma.

Pelvic MRI done:

Bulky pre-sacral retro-rectal mass invading the last sacral parts and intimately linked to the pelvic floor and measuring 14 cm on the long axis. ---> radiological aspect evoking in the first place a chordoma with pre-sacral development (Figure 1).

Pathological anatomy

CT-guided biopsy: histological and immunohistochemical aspect compatible with chordoma.

Patient refused surgery given the locally advanced nature of the tumour.

The patient received an external RTH: Dose received: 54 Gy in 02 series: 40

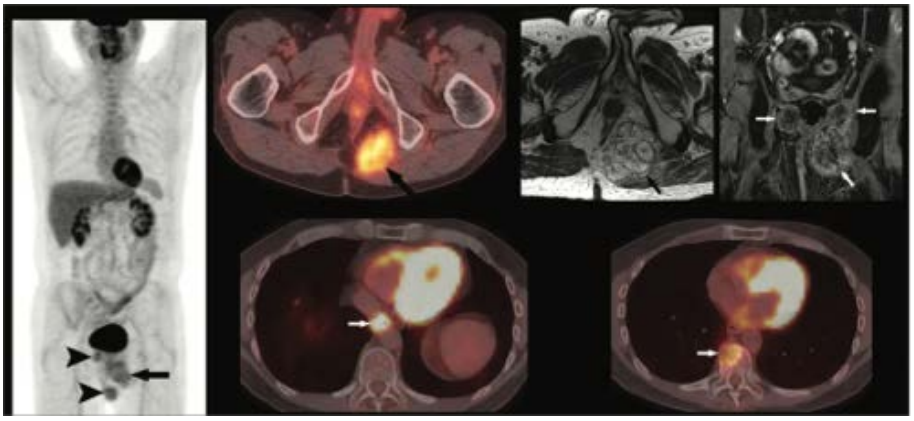

Figure 1. Initial radiological exploration case 1.

Gy in 20 fractions of 2 Gy + supplement of 14 Gy in 7 fractions of 2 Gy.

Evolution

6 months after the end of the radiotherapy, the patient presented with pain next to the sacral region with the impossibility of lying down or in a sitting position with, on abdominal palpation, the perception of a large mass in the left hypochondrium., painless, mobile with respiration.

Control CT TAP:

Bulky locally advanced pre-coccygeal pre-sacral tumor mass with secondary hepatic locations.

Suspicious LSD lung nodule.

Therapeutic decision:

Patient put on imatinib 800 mg/day with good tolerance.

Symptom improvement and sustained partial radiological response for up to 2 years, then patient presented with lameness with sacral pain.

Evaluation TAP scanner objectified an increase in size of the osteolytic tissue mass of the left iliac wing breaking the cortex, with stability of the imaging in addition.

Transition to a second line with sorafenib, with clear and rapid progression after 3 months, with decision to put cisplatin imatinib in 3rd line, but unfortunately, clear progression 3 months later at the level of the primary tumor and bone and hepatic localizations, with appearance peritoneal locations.

Decision to switch to a new therapeutic line with pembrolizumab, but since then the patient has been lost sight of.

2.2. Case 2

74-year-old patient, with no notable pathological history:

History of the illness: began with the appearance of urinary incontinence for which the patient consulted a urologist.

Imaging

a pelvic MRI was requested:

voluminous sacrococcygeal osteolytic process measuring 145 × 180 mm, locally advanced, with sacral intraductal extension and to the gluteal muscles.

MRI aspect compatible with a sarcomatous process.

TAP CT: locally advanced sacrococcygeal lytic expansive process measuring 16.8 * 3.1 * 14.7 cm, without distant metastasis (Figure 2).

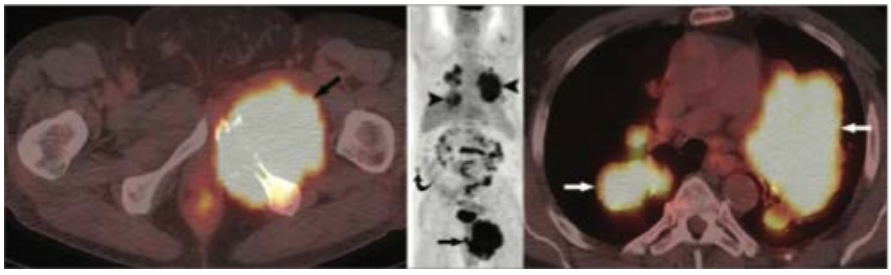

Figure 2. Initial radiological exploration case 2.

Pathological anatomy

Biopsy performed: Appearance suggesting a grade 2 chondrosarcoma; according to O'Neal and Ackerman.

Proofreading blocks:

histological and immunohistochemical appearance consistent with chordoma.

Physical examination:

PS at 2

has urinary incontinence

painful mass next to the left iliac crest

free nodal areas

Therapeutic conduct in CPR

patient refused surgery and received palliative HRT at a total dose of 20 Gy.

put the patient on Imatinib

Evolution

after 6 months of treatment, the patient presented a partial radiological response with improvement of symptoms.

on the day of writing this article, the partial partial response is still maintained with a very good tolerance to imatinib.

3. Discussion

Chordoma is globally a very rare tumour. Its incidence varies between 0.5 and 8 cases per million inhabitants and per year [1]-[6]. It represents 1% to 4% of primary malignant bone tumors [2]. Chordoma can be seen at all ages, with a median age of diagnosis of 58.5 years and the incidence increases gradually with age [2]. Men are significantly more affected than women (sex-ratio M/F = 3/1) [7]. In our case, it is a 58-year-old woman. Chordoma is a tumor of embryonic origin. It results from the proliferation of persistent cell islands in the vertebrae or the base of the skull. These cell islands are embryonic remnants.

The pathology examination is a fundamental and essential element for the diagnosis of chordomas as well as for all bone tumors. According to the WHO: "chordomas are malignant tumors with notochordal differentiation". Macroscopically, it is a generally lobulated tumour, of soft gelatinous consistency, grayish or bluish-white in color [2]. Microscopically, the tumor cells are large in size, with a well-delimited cytoplasm, homogeneous or clarified eosinophilic, containing one or more optically empty vacuoles pushing back the nucleus, sometimes deforming the cytoplasm realizing the aspect of physaliphore cell or spider cell. These cells are grouped in cohesive clusters of variable size, or form single-cell trabeculae, or isolated cells, on a myxoid matrix of highly variable abundance from one tumor lobule to another within the same tumor. The nuclei are variable in size and outline, somewhat irregular and hyperchromatic. Mitosis, haemorrhagic or necrotic inflammatory changes, sometimes extensive, and apoptosis can be observed [2]. In chordomas, pancytokeratins and cytokeratin 19, EMA (epithelial-membrane antigen) and vimentin are almost constantly ex-

pressed, but sometimes only focally. Brachyuria is a more recent marker [8], very specific for chordoma with a sensitivity of around 90.2% [2].

For our case, the immunohistochemical study: AE1/AE3: diffuse positive staining of tumor cells; EMA: focal positive staining of tumor cells; PS100 and vimentin: focal positive staining of tumor cells. The clinical signs depend on the size and location of the tumour. They are generally late due to the slow evolution of these tumors and are non-specific [7] [8]. The clinical signs are often dominated [9] by pain, the most frequent revealing sign. This pain is secondary to compression and/or invasion of neighboring organs. Digestive disorders (rectal syndrome, constipation, occlusive syndrome, etc.). Urinary disorders: pollakiuria, dysuria, urinary incontinence…Neurological disorders: which are secondary to compression or invasion of the various nerve plexuses and nerve roots in the region. In 97% of cases, inspection of the perineum reveals the presence of gluteal or posterior perineal swelling or filling of the presacral region evoking a retrorectal tumor [10]. Digital rectal examination often shows a presacral mass with a firm, painless, sometimes lobulated, fixed, rough consistency [8]. It allows to appreciate the size, the seat in height compared to the sphincter apparatus and the upper limit, it also allows to control the perineal sensitivity to eliminate nerve damage [9]. In our case, digital rectal examination revealed rectal stenosis by compression of a posterior mass.

Modern imaging techniques occupy an important place in the paraclinical assessment of sacral chordoma, making it possible to evoke the diagnosis, characterize it and above all to study its relationships. Abdomen plain images (ASP), as well as those centered on the pelvis, front and profile: although there are no pathognomonic radiological signs, chordomas are generally considered to have four main characteristics: expansion - bone rarefaction - intratumor trabeculations - calcifications [10]. CT is of great interest both in the pre-therapeutic assessment and for monitoring [8], it makes it possible to specify the nature of the mass, to appreciate its character, its topography and its limits, and possibly its locoregional and remote extensions. [10]. Destruction of sacrococcygeal bone associated with a tumor mass that is often bulky with sharp edges, the density of which approaches that of soft tissues [11] [12] has been described. Pelvic MRI alongside CT provides great topographical precision, particularly for the soft tissues, the epidural and intradural space (nerve root damage) and makes it possible to assess the liquid or solid component of the lesion, its contiguity with the rectum, its limits, and therefore evoke the diagnosis while determining the best surgical access [2]. The value of 18FDG positron emission tomography (PET-scan) lies in the differential diagnosis between chordoma (null uptake) and metastasis (intense uptake and sometimes multiple lesions) [2].

Several lesions can mimic sacral chordoma such as chondrosarcomas, giant cell tumors, aneurysmal cysts, Ewing's sarcoma, myxopapillary ependymoma, and bone metastases [2] [8] [10], including radiological, histological data and immunohistochemistry make it possible to rule them out. The only chance of

cure rests on an "en bloc" surgical resection, with excision limits in the healthy zone [8]. Nevertheless, the tumor recurrence rate remains relatively high [2]. This type of resection is generally easier to perform when the tumor sits below the first 3 sacral vertebrae.

We also know that extended sacrectomies above S3, including part of the sacroiliac joints, are technically difficult and frequently lead to complications, in particular sphincter disorders and gait disorders [12]. These excisions are sometimes difficult and hemorrhagic, in the case of large tumors, therefore they must respect the stability of the pelvis and avoid neurological complications. To perform a wide and en bloc resection, a posterior approach is most often proposed for chordomas not exceeding S3. On the other hand, a combined anterior and posterior approach is used for those exceeding S3 [13].

Radiotherapy finds its place either as an adjuvant after surgery, or exclusively in the event of local recurrence, or even when surgery is impossible [14]. In view of the high relapse rates obtained after exclusive surgery, adjuvant photon irradiation was initially proposed, however progression-free survival was always less than 40%. The proximity of the organs at risk to the tumor and the ballistic properties of the photons often prevented delivering doses greater than 60 Gy to the tumor, which directly impacted local control [2]. Chordomas have variable radiosensitivity, but in most cases they are radioresistant tumors [14]. This raises questions about the indication of adjuvant radiotherapy, which finds its place after R1 and R2 surgery at a dose of 50 to 60 Gy in 5 to 6 weeks. Radiotherapy is sometimes indicated exclusively and palliatively, in the case of very large, non-operable tumours. A first series of external irradiation for decompressive and analgesic purposes is delivered up to a dose of 50 GY in 5 weeks. In the event of a good objective tumor response to the control tomodensitometric examination, additional external irradiation of 20 GY can be performed in 2 weeks.

Exclusive external irradiation only exceptionally leads to complete tumor destruction, on the other hand, good comfort is often obtained and above all a good analgesic effect. Given the possibility of occurrence of metastases, chemotherapy combinations have unfortunately been tried without success [15]. Proton therapy makes it possible to increase the dose in the tumor and to spare the neighboring critical organs as much as possible thanks to the ballistic characteristics of the protons [2]. This physical peculiarity is fundamental to explain the dose gradient that can be obtained near a critical organ. The dose varies from 10 to 15% per millimeter of tissue crossed [16]. It was then shown that local control was improved and the risk of toxicity acceptable in a large number of series. This is why, for several years, proton irradiation has become the reference irradiation technique in the management of chordomas of the base of the skull after surgery [16]. The use of carbon ions represents an interesting modality. Indeed, they have the physical advantages of protons (Bragg peak) and a relatively superior biological efficiency, interesting for radioresistant tumours. Promising results have been obtained in Japan and Germany in terms of efficacy and also in terms

of toxicity [14] [17].

The experience of chemotherapy has most often proved to be disappointing, but it nevertheless seems useful to use it in secondary localizations of the disease [2].

In practice, the chemoresistance of these tumors is recognized even if positive and isolated results have been reported with anthracyclines, alkylating agents, cisplatin and thalidomide [2] [18]. Also imatinib alone or combined with sirolimus has shown some efficacy in terms of local control in PDGF-expressing chordomas [19] [20]. The prognosis of sacral chordomas depends above all on the quality of the surgical excision. Apart from complications related to the surgical act itself, secondary complications can occur such as local recurrences which are a pejorative event significantly reducing the overall survival of patients [2]. The interest of radiotherapy remains debated because the majority of case series did not reveal any major effect on survival [15]. To date, radiotherapy is suitable for locally controlling the tumor, but the real ability of adjuvant radiotherapy to improve recurrence-free and overall survival remains unknown. The mean survival in Erikson's series was 6.6 years for the radiosurgery group, compared to 5.7 years for surgery alone and 5.4 years for radiotherapy alone. In our case, after 2 years from the end of radiotherapy, the patient is still alive with less pain and clinical and radiological stability of the tumour.

4. Conclusion

Adult sacral chordoma is a rare entity. They are developed from embryonic residues, remnants of notochord. Diagnosis is very late due to clinical latency, of which pain is the main symptom. The positive diagnosis is based on clinical and imaging with confirmation by pathological examination. The basic treatment is surgical, and must consist of total excision as far as possible in order to avoid both complications and recurrences. Radiotherapy is used as a complement to surgery, immediately or in the event of local recurrence, or even exclusive radiotherapy, when surgery is impossible. Sacral chordoma is characterized by its malignant potential with a high risk of local and locoregional recurrence, on the other hand, metastases are late.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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