

# Studies on Brain and Spinal Cord Tumors

## Chapter 1

### Osteochondroma of the Spine

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#### Abstract

Osteochondroma (OC) is the most common benign tumor of the bones, and it remains the most common precursor for secondary chondrosarcoma, which often occurs in the long bones' metaphyseal areas. Rarely, it is also found in the spine. This tumor comprises a cartilage capped bone projection and is observed in both solitary and multiple forms. In many cases, the lesion can be definitively diagnosed according to radiological characteristics, but the rarity of these lesions in the spine, gradual onset of symptoms, and the frequent lack of observation of lesions in plain radiography may delay the diagnosis or cause misdiagnosis. These lesions are benign and do not risk the patient's life; however, they rarely may be found to be a malignant degeneration that transformed into chondrosarcoma. When the lesion has led to clinical symptoms or has faced the patient with cosmetic challenges, or when definitive diagnosis is unknown, treatment is required. The primary treatment is the surgical removal of the lesion. Timely diagnosis and complete resection of the lesion using surgery lead to complete recovery and prevent recurrence.

#### 1. Introduction

According to the World Health Organization's (WHO's) definition in 2002, osteochondromas are benign bone neoplasms covered by a cartilaginous cap created at the outer surface of the bone by endochondral ossification [1]. Osteochondroma (OC) is the most common benign primary tumor of the bone. This tumor may be observed in 3% of the total population [2] and accounts for 10-15% of total bone tumors and 20%-50% of benign bone tumors [3]. These lesions are classified into either solitary or multiple forms. The solitary form accounts for 85% of cases, and the multiple form, which is hereditary, makes up 15% of cases [2]. OC can arise from any endochondral bone [4]; it is not only observed in the bones of the face and skull [5], but it usually occurs in the metaphyseal proximal humerus, distal radius and ulna, proximal tibia, and the distal femur [3]. Although this tumor can also affect the spine,

the occurrence of spinal OC is rare [6]. According to the literature, the involvement of the spine occurs in 1.3%-4.1% of cases in the solitary form and 7%-9% of cases in multiple forms [6,7,8]. Since most of these lesions are asymptomatic, they may never be diagnosed, and the prevalence of spinal OC may be underestimated [9].

## 2. OC of the Spine

Spinal OC is a rare condition but is a cause of neurological symptoms and/or complications, and its diagnosis is difficult due to its rarity, the gradual onset of symptoms, and its invisibility in radiography images [10]. OC begins through endochondral ossification of the ectopic cartilage in the end plate. Due to various causes, such as trauma, a segment of the epiphyseal plate is separated from its normal location and is subject to hernia from the periosteum adjacent to the growth plate. Next, this separated segment grows diagonal to the long bone axis and far from the adjacent joint [2,11]. The prevalence of this tumor in the cervical spine is related to the increased movements within this segment, and thus additional micro-trauma to the epiphyseal plate and increased separation of the epiphyseal plate [12]. OC growth occurs at the lesion's helm with calcification of the cartilaginous area [13]. Since most spinal OCs grow out of the spinal canal, the occurrence of spinal cord and nerve compression are extremely rare [10,14] and only 0.5%-1% of spinal OCs have been associated with spinal cord or nerve roots' compression, which lead to neurological complications [10]. In addition, spinal cord compression is twice as likely in multiple forms [10].

Although OC can arise from any part of the vertebral body, most commonly it arises from the posterior elements, including the pedicle, lamina, or articular processes and presents as a slow-growing, painless mass. The high incidence of tumors in these areas may be related to the multiple secondary ossification centers [10,12] that appear at the age of 11 to 18 years [10]. The cartilage of these secondary ossification centers may become an origin for the creation of abernethy's cartilage, and the tumor may be created during its growth. Whatever these ossification centers are ossified faster, the possibility of creation of abernethy's cartilage and thus OC is more for them [15]. Ossification of these secondary centers is faster in the neck and thoracic region and occurs during adolescence, while ossification occurs in the lumbar region at the end of the second decade of life [16]. This ossification process is probably one of the causes for the common presence of tumors in the neck and thoracic region. Vertebral bodies rarely comprise the origin of tumor creation, primarily because of the lack of an epiphyseal plate in this area [10]. Radiation also causes OC [17], and OC is the most common benign tumor that occurs after radiotherapy [18]. In these cases, the damaging effects of radiation on the epiphyseal plate causes the undifferentiated cartilage tissue to immigrate to metaphysis and create a tumor [19]. These tumors are usually of a single type and are generated at the irradiation site. In 12% of children who have experienced radiotherapy in childhood due to a malignancy, such a tumor may be observed [20]. The amount of radiation required to create a

tumor is not precisely known, but if children less than 2 years old are exposed to 25 Gy or more of radiation, such tumors may occur in 12-15% of these children in the future [21]. The length of time between the radiation event and tumor formation has been reported to be between 17 months and 9 years [22]. Some cases of OC have been reported following surgery and trauma too [23,24]. Trauma and surgery are likely to create ectopic cartilage in the end plate and their endochondral growth may generate a tumor.

### 3. Epidemiology

As already mentioned, this disease is observed in both solitary and multiple forms. The multiple form of the disease is recognized with the presence of two or more OC in the long bones [25]. This disease is also called by other names, such as hereditary deforming chondrodysplasia, Ehrenfried disease, multiple chondromatosis, multiple cartilaginous exostoses, dyschondroplasias, Bessel-Hagel syndrome, and diaphyseal aclasis [10]. The presence of multiple-form OC in the Caucasian population, which is the population under thoroughly study, has been reported in 0.9–2 people per 1,00,000. However, in isolated populations, such as Guam and the Ojibway Indian islands, the OC occurrence rate is extremely high, ranging from 100–1310 people per 100,000 respectively [26]. The multiple forms are a hereditary disease that is transmitted as an autosomal dominant with an incomplete penetrance in women [10] with 50% of children affected by it [25]. The number of lesions varies in different families with an average of 15–18 per person [25]. In this disease, multiple OCs appears in different areas of the body, which are often accompanied by pain. Since they commonly occur around the joints, OCs may be accompanied by deformities of the joints and skeleton, restriction in the movement of the joints and skeleton, and bone shortening (**Figure 1**). Moreover, the compression of blood vessels and nerves by tumors may also lead to symptoms. In its multiple forms, the possibility of involvement of the spine and neurological complications are higher compared to solitary form [8]. Additionally, OCs have been reported more frequently in the lumbar region (34%), followed by the cervical region (23%) [13]. With the involvement of the spine in the multiple form, despite multiple lesions in different parts of the body, the spinal lesion is typically solitary [1]. In a study conducted by Bes et al. [27], the average age of patients with OC was 28.5 years, and the age of those manifesting with neurological symptoms was 29.7 years. Patients with multiple forms of the disease that manifest with neurological symptoms were much younger (22.3 years old compared to 36 years old).

In the solitary form, the cervical spine is the most common involvement site, followed by the involvement of the thoracic and lumbar regions [28]. According to Albrecht et al. [29], more than 50% of the OCs originate in the cervical spine. Both the solitary and the multiple forms are more common in men than in women (2.5: 1 ratio) [10].

#### 4. The Role of Genetics in Creating OC

The influence of genes is proven for the multiple form of OC. OC is one of the most common hereditary musculoskeletal diseases, and its prevalence is 1 in every 50000 births [3], and 62% of patients have a positive family history of the disease [30]. Thus, the disease is categorized as both familial and sporadic. Both the sporadic and familial forms have been reported more commonly in males [14,18], which indicates incomplete penetrance in females [18]. Incomplete penetrance in females may be caused by hormonal influences or possibly the X-link moderating gene. Most OC cases are diagnosed in children up to the age of 5 years, and virtually all have been diagnosed by 12 years [3].

The disease occurs as a result of changes in two genes: exostosis (multiple) -1 (EXT1), located on chromosome 8q24.11-q24.13, or exostosis (multiple) -2 (EXT2), found on chromosome 11p11-12 [75-81] [2]. Another case reported abnormalities in the EXT3 genes located on the short arm of chromosome 19. However, in most cases, multiple OCs are related to the first two genes [31], while 44%–66% of the familial form are related to EXT1 and 27% of them are related to EXT2 [30]. Most reported hereditary multiple OCs are heterozygous for the mutation in one of the EXT genes [32]. EXT1 is associated with one of the most severe forms of the disease [33] and has the highest probability of malignancy [33,34]. Some mutations in these genes have been reported in Caucasian and Asian populations [30]. Since there is no family history in 40% of patients, this mutation may explain the cases in which the patient has no family history of OC [1]. In addition, some cases of the biallelic inactivation of the EXT1 gene in solitary (nonhereditary) forms of OC have been reported [32]. Somatic mutation is extremely rare in genes and is only found in the cartilage cap of the tumor [32]. The observation of gene mutation in the cartilage cap, without observing it in the perichondrium and bony stalk, indicate that the cartilaginous cap is a neoplastic part of the lesion, in both the multiple and solitary forms of the disease. Furthermore, it is now proven that these tumors originate at the growth plate rather than the perichondrium, as some researchers previously suggested [32]. Somatic gene mutation is only found in the EXT1 gene, and nothing has been reported on the EXT2 gene [32].

These two genes act as tumor suppressors [30], and the final impact of these genes is focused on the synthesis and transmission of a complex hybrid that occurs in the Golgi apparatus [30]. This effect interferes in the production of a glycosyltransferases enzyme [25] in the synthesis of heparan sulfate proteoglycan [2]. In this case, although the heparan sulfate proteoglycan is synthesized, it accumulates in the Golgi apparatus instead of being transferred to the cell surface and exerting its proper effect [25]. Heparan sulfate is a macro protein with different functions that regulate the growth paths in the epiphyseal plate [2]. As a result of this substance not reaching the cell surface, the creation of receptors that bind to factors, such as fibroblast growth factor, is avoided, and the normal growth of cartilage is disrupted [25]. Simi-

lar to the multiple forms of the disease, genetics, and mutation are likely to play a role in the solitary form. In a study by Hameetman et al. [32], seven out of eight patients with solitary OC expressed changes in the EXT1 gene that were uniquely associated with the cartilaginous cap of the lesion. According to this study, the cartilaginous cap was the tumoral component of the lesion, and its bony stalk was reactive.

## **5. The Clinical Manifestation of the Spinal OC**

Most spinal OCs are asymptomatic and rarely lead to neurological symptoms [35,36]. A few cases of OC have also been reported among the elderly [37], and some researchers believe that OCs of the spine also continue to grow after puberty [7]. However, the prevalence of this lesion reduces with age [4], and the growth of these lesions stops with stunted growth or the closure of the epiphyses [4,18]. When OC becomes symptomatic at older ages, several possibilities must be considered. The first probability is that the OC transformed into a malignancy. Due to tumor growth, the size of the lesion increases and symptoms appear. Accordingly, in OC manifested in older people, necessary examinations must be carried out in terms of conversion to malignancy [10]. Another cause may be the addition of degenerative spine disease and disc herniation on the lesion and creation of symptoms [38]. Yagi et al. [39] explained three cases of OC in older people, which created symptoms through the addition of chronic inflammation brought on by other diseases, such as psoriatic arthritis. Clinical manifestation of the lesion may occur with pain or local swelling; in many cases, and patients remain free of neurological symptoms. The symptoms gradually began in most cases, and there was typically a long time between the emergence of symptoms and the diagnosis of the disease (9), which has been reported to be 3.9 years on average [36]. The lesion growth into the spinal canal or neural foramen can lead to radicular pain, spinal stenosis, and myelopathy, or a spinal cord lesion. Due to the gradual growth of tumor, the symptoms appear progressively in most cases, and accurate and prompt diagnosis requires high index of suspicion [40]. But in rare cases, the onset of acute symptoms has also been reported [41]. In OC of the neck following sudden hyperextension or falling, acute symptoms may appear [9]. In the neck, where a lesion originated from a vertebral body and grows toward the anterior, rare symptoms such as dysphagia, sleep apnea, vertebral [4], subclavian [9], common carotid [42] artery occlusion, restrictions on the movements of the neck [43], and Horner syndrome [44] can also be observed. In patients with multiple hereditary exostoses, who are referred to medical centers with vertebral column pain or neurological deficits, spinal OC must be investigated.

## **6. Radiologic Characteristics**

In addition to diagnosis, radiological surveys also have an important role in determining any surgical plan, and thorough radiological examinations must be performed.

## 6.1. Radiography

The diagnosis and assessment of spinal OC using plain radiography is difficult due to the overlapping of various structures of the spine in different projections [10,35]. However, in cases where the lesion is visible on plain radiography, it is observed as a round or oval bone mass with well-defined borders (**Figure 2**). Plain radiography may be diagnostic in 21% of patients [45]. The lesion may be pedunculated or sessile and in the spine sessile form is more common. Due to the inability to see cartilage in radiography, the lesion actual size is larger than its value depicted in the radiograph.

## 6.2. CT Scan

CT Scan, with the injection of an intrathecal contrast (CT myelography), is the preferred method for the evaluation of spinal OC [10,46]. Because of the bony nature of the lesion, a CT Scan defines the tumor better than an MRI. Moreover, a CT Scan shows a well-circumscribed bone mass with a sharp border and lucent medullary area, in which both are continuous with the parent bone (**Figure 4**). The continuity of the cortical and medullary portions of the lesion with the parent bone is pathognomonic for the diagnosis of OC [10,47]. The existence of calcification or lytic areas can better be diagnosed with CT Scan. However, the thickness of the cartilage cannot be evaluated by this method and is estimated to be less than the actual amount [20,48]. Various researchers believe that the following characteristics, when found in a CT Scan, can help diagnose OC:

- A round well-circumscribed mass.
- Bone density with dispersed calcification.
- A paraspinal, or dumbbell, or eccentric mass in the spinal canal.
- Osteosclerosis changes in the adjacent bone.
- Lack of contrast enhancement [9,49].

CT Scan also is very important for determining a surgical approach because CT images reveal the lesion size, location, origin, and its extension into the spinal canal.

## 6.3. MRI

The relative limit of an MRI compared to a CT scan comprises its lack of sensitivity to minor calcifications, which can lead to diagnostic errors. However, MRI is useful in the diagnosis of the lesion and its compression of the spinal cord. Moreover, the cartilaginous component of the lesion and its thickness are better diagnosed by MRI [20]. MRI is also convenient for the detection of lesion recurrence and malignant transformation. The presence of a cartilaginous component is necessary for diagnosis of OC, and the appearance of a significant thickness may depict malignant degeneration and chondrosarcoma. On an MRI, the cartilaginous component

is iso- to hyperintense in T1-weighted sequences and hyperintense in T2-weighted sequences [21]. This cartilaginous component lacks enhancement after injection of contrast material. In some cases, contrast enhancement may be seen around the lesion, which occurs because of the enhancement of fibrovascular tissue surrounding the lesion. Measuring the thickness of the cap is important in OC. In a study by Hudson et al. [50] of skeletal OCs, the average thickness of the cap was 9 mm, and this thickness is much higher in chondrosarcomas. In cases where the cartilage thickness is greater than 2 cm [15], malignancy should be considered more likely, but a definitive diagnosis requires a biopsy. The following radiologic findings are indicative of transformation to malignancy: tumor growth after the closure of the growth plate, changes of the tumor border, lytic areas within the tumor, the destruction of adjacent bone, and the existence of soft tissue containing calcification [33].

In the study of OCs by MRI, we see a peripheral rim with low intensity that reveals the cortical bony component outside the lesion; while in the central portion, there is an intermediate signal resulting from bone marrow that creates a “bull’s-eye” design [10]. MRI also shows the extension of cortical and medullary portions of a lesion with the cortical and medullary portions of the parent bone from which they originated, which aids the diagnosis of the lesion’s nature. Regarding the cases of sudden death [51] and acute neurological complications, Roach et al. [52] recommended that in all patients with multiple OCs at the age of 4 years, the entire of spinal column must be examined using MRI to prevent such complications through the early detection and treatment of lesions.

#### **6.4. Scintigraphy**

Bone scintigraphy can be used to determine the stage of the lesion, while also excluding metastases [9]. In adults with low or halted lesion growth, lesion metabolism is low, and this finding favors the likelihood of a benign lesion [2]. Moreover, nuclear medicine has been helpful in the diagnosis of multiple lesions [53].

### **7. Treatment**

Given the low probability of lesion malignancy (less than 1%); if the patient is asymptomatic, the lesion can be controlled. In cases where the patient suffers from pain or neurological complications due to a tumor, or when a lesion’s pathology is unknown, surgical removal of the lesion should be attempted. Rose et al. [51] reported a case of sudden death after a minor trauma in a patient with an OC at the C2 level. Therefore, in cases where the lesion is associated with a noticeable spinal cord compression, particularly in the upper part of the neck, which may influence nerves associated with life-threatening complications, prophylactic removal of the lesion is recommended [35].

Due to the location of the lesion, a posterior approach and laminectomy are often used.

To reduce the effects of laminectomy, particularly in the cervical area, various methods can be employed simultaneously with the removal of the lesion, such as laminoplasty. When surgery leads to instability caused by facet degradation, or in a young patient with a cervical lesion and cervical kyphosis, posterior fusion must be attempted at the same time. When possible, the lesion should be completely removed. Intralesional excision should be avoided because it is associated with a high risk of disease recurrence [27]. The bony nature of the lesion and working among the sensitive structures of the spinal cord and nerve roots frequently prevents complete removal of the tumor in one piece. Therefore, the lesion is removed piece by piece using a chisel and a high-speed bur. Complete removal of the cartilaginous cap should also be attempted because this removal prevents lesion recurrence. The overall incidence of recurrence in solitary OC of the spine is less than 2% [9], but incomplete removal of the cartilaginous cap results in a recurrence rate of up to 50% [13]. Recurrence may occur from 6 months to 14 years after surgery [13], but the average time from the original surgery to recurrence is 2.4 years [10]. The primary activity at recurrence is to define possible malignant degeneration of the lesion, which must be fully investigated, and the necessary treatment measures should be performed promptly. When the lesion is aggressive, the surgeon should try for an “en-block” excision of the lesion.

When the lesion grows out to the anterior side of the cervical or thoracic spine, and causing spinal cord compression from the anterior side, we have to use an anterior approach. In these cases, corpectomy and fusion with an instrument are required.

In cases where a malignant pathological lesion is discovered, the use of radiotherapy is ineffective, but radiotherapy may play a role in differentiating of the malignancy of the tumor [22].

Where OC causes neurological symptoms with spinal cord compression, followed by uncomplicated removal of lesions, significant improvement of symptoms can be expected.

## 8. Pathology

Lesions may be pedunculated or sessile and be covered by a thin cartilaginous cap. The cartilage cap covers the surface of the lesion in a smooth, shiny blue-gray coating (**Figure 5**). If the thickness of the cartilaginous cap is more than 2 cm and irregular, malignancy of the lesion should be considered. During microscopic examination, the cartilage area is integrated with the underlying bone and is covered by a thin layer of fibrous tissue that forms the perichondrium. This perichondrium follows the periosteal of the bone from which it originated [32]. The cells in the cartilaginous area is similar to the growth plate and is formed from the masses of chondrocytes. The number of chondrocytes is typically slightly higher than normal, and some of them are poly-nucleic. The bony cortex of the lesion is the same as the cortical bone from which it originated. Accordingly, the medullary cavity of the lesion follows along



the bone from which it originated. Irregular mineralization, the existence of a soft tissue band, a highly irregular surface, cystic changes, the loss of cartilage architecture, myxoid changes, necrosis, increased cellularity, mitotic activity, and atypical chondrocytes indicate malignancy [2].

## 9. Complications

One of the complications associated with this disease is malignant degeneration and the creation of secondary chondrosarcoma. Chondrosarcoma is the most common primary malignant bone tumor and 6–10% of chondrosarcomas occur in the spine [54]. According to the literature, 0.4–2% of solitary OC and 1%-4% of the multiple OCs may convert to chondrosarcomas [3]. However, two-thirds of the secondary chondrosarcomas originate from a solitary OCs, while one-third of them originate from multiple OCs [2]. This is simply due to the higher prevalence of solitary OCs.

The most common location for the occurrence of spinal chondrosarcomas is the thoracic region. Additionally, spinal chondrosarcomas are more prevalent in males and are often found among adults. These tumors are rare among people less than 21 years old [54]. The average diameter of spinal chondrosarcomas is 5.5 cm, which is less than the average for peripheral chondrosarcomas (femur, 11 cm; pelvic, 13 cm). This size discrepancy exists because the early symptoms of a spinal column chondrosarcomas [54] are more noticeable. Although malignant degeneration is rare, even in multiple forms, OCs are one of the very rare pre-malignant cases that can eventually create sarcomas [2,55]. In patients with OC, sharp increases in the size of a lesion and the appearance of symptoms, such as pain, can be indications of the OC's transformation into a chondrosarcoma [8]. Recurrence of the lesion after surgery can also be a symptom of the OC's transformation to a chondrosarcoma [13].

The best criterion for determining the malignancy of a lesion is the thickness of the cartilaginous portion of the tumor [28], specifically in peripheral OCs [56]. According to Wörtler et al. [57], if the thickness of the cartilaginous OC is more than 2 cm in adults or 3 cm in children, malignancy must be suspected. However, the thickness of the cartilaginous area of spinal OCs has not been investigated. MRI is the best method for imaging the thickness of cartilage [27,58]. The following characteristics found during radiologic investigations are common signs of chondrosarcoma: lesion growth after the closure of the growth plate, delineation compared with previous imaging studies, lytic areas within the lesion, destruction and erosion of the adjacent bone, the existence of a soft tissue mass containing dispersed and irregular calcifications [10], irregular margins of the lesion [59], a lobulated lesion, and a periosteal reaction [2]. If the MRI is carried out with contrast material, observing septal enhancement is indicative of chondrosarcoma, while the peripheral enhancement [60], or mild medullary enhancement [36,60,61] may be observed in OCs. Chondrosarcoma are treated by complete

surgical removal. The most important prognostic factor for local control of chondrosarcoma is wide or marginal resection of the tumor [54]. Radiotherapy and chemotherapy are not used in these patients either as early treatment or adjuvant therapy [54].

## 10. Postoperative Complications

Postoperative complications include the creation or exacerbation of neurological deficits, bleeding, and deep vein thrombosis; similar complications are also observed in surgery for other spinal tumors [54].

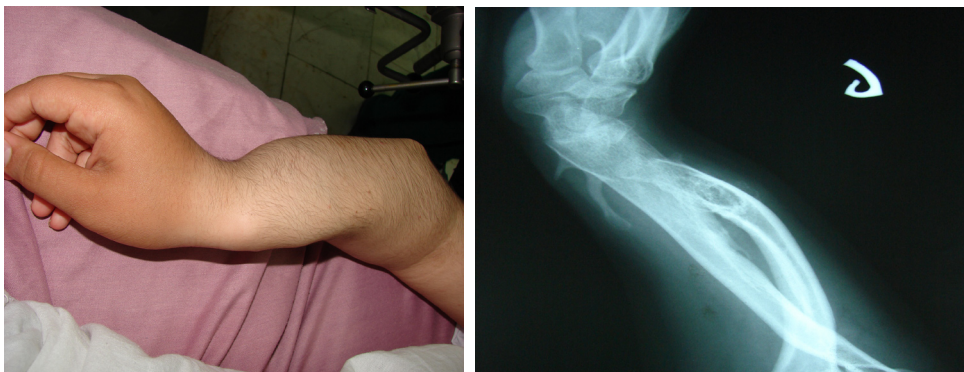
## 11. Prognosis

If complete removal of the lesion without complications occurs, neurological improvement will be observed in 81% of cases after surgery [36].

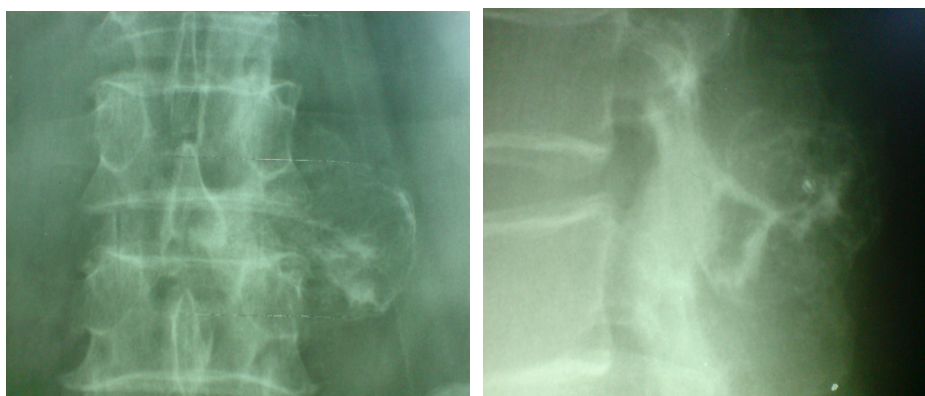
## 12. Conclusion

Although OCs is one of the most common bone tumors, they rarely involve the spine. On rare occasions, these lesions cause compression of the spinal cord and nerve roots. These lesions are seen in both solitary and multiple forms of the disease, and the multiple form is frequently observed at younger ages and is associated with increased neurological complications. In symptomatic cases, surgical total tumor resection without complications leads to the patient's improvement.

## 13. Figures



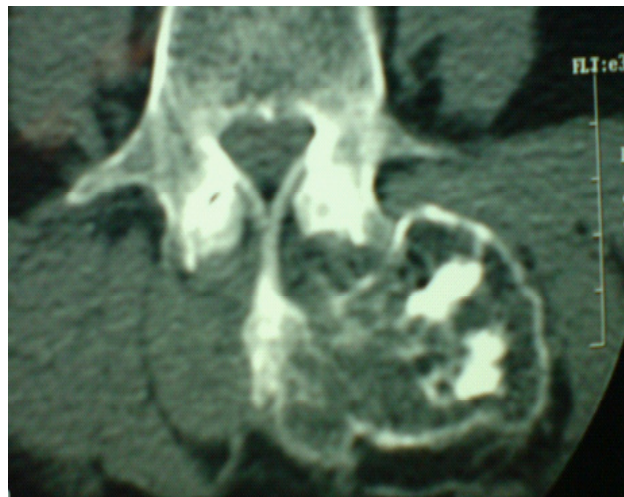
**Figure 1:** (A) hand deformity and (B) its plane radiography, in a patient with multiple form of the disease.



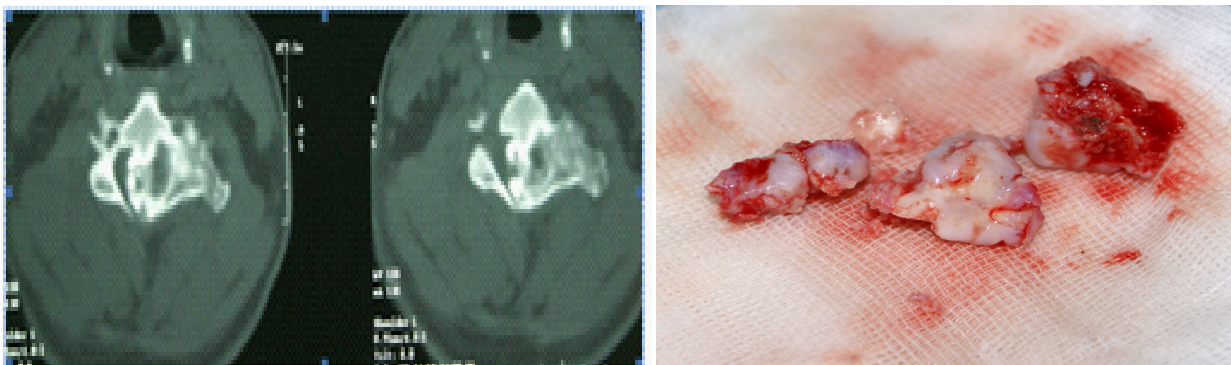
**Figure 2:** Antero-posterior and lateral radiography of a patient with lumbar osteochondroma.



**Figure 3:** CT scan of sessile osteochondroma



**Figure 4:** Osteochondroma originating from the spinous processes of a lumbar vertebrae. Note that the medullary and cortical portions of the tumor follow along with the parental bone from which they originated.



**Figure 5:** CT scan (a) and the bone lesion removed from the patient's body (b). Note that the lesion's surface is covered by shiny cartilage.

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