



# A Case of Pain Insensitivity Syndrome Mimicking Osteosarcoma

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## Abstract

Congenital Insensitivity to Pain with Anhidrosis (CIPA) is a rare autosomal recessive inherited condition that severely affects the peripheral nervous system. It leads to a decrease in myelinated nerves and loss of unmyelinated ones. This results in pain insensitivity, anhidrosis, intellectual disability, and repetitive involuntary injurious movements; such as oral self-mutilation, biting of fingertips, bruising, and scratching which predispose the skin to various infections. Clinical findings and biallelic pathogenic variants in NTRK1 (neurotrophic receptor tyrosine kinase 1) are important in diagnosis. No cure is available and the treatment is supportive.

Here, we report an atypical case of a 4-year-old female patient who presented with a swelling in her left leg, whose detected bone mass was misdiagnosed as an osteosarcoma with predominant chondroblastic features. During her follow-up, only after her second presentation with multiple bone fractures, she could finally be diagnosed as CIPA. The patient was initially followed up after a short period of chemotherapy with the diagnosis of osteosarcoma. Upon her next presentation with swelling in the same leg with multiple bone fractures, the biopsy was repeated, and this time it was diagnosed as an exaggerated callus formation, a major pathological mimicker of chondroblastic osteosarcoma, and then, a final diagnosis of CIPA was reached, genetically.

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## Introduction

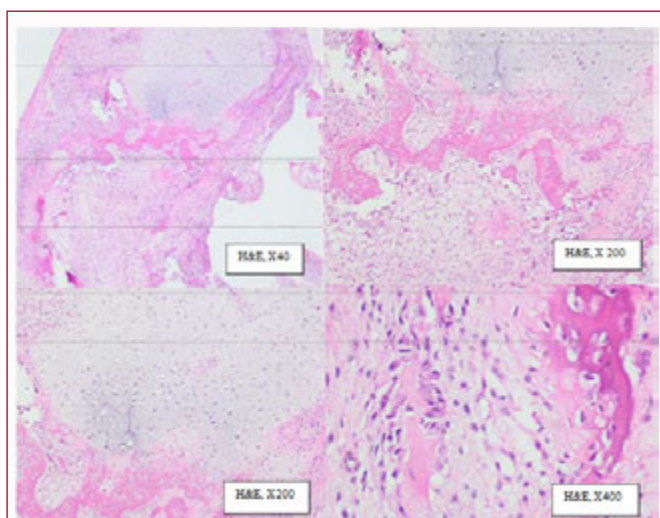
Congenital Insensitivity to Pain with Anhidrosis (CIPA), also known as Hereditary Sensory and Autonomic Neuropathy (HSAN) type IV, is a rare condition with autosomal recessive inheritance that severely affects the peripheral nervous system and leads to a decrease in myelinated and loss of unmyelinated nerves [1]. Hereditary sensory and autonomic neuropathies are a clinically and genetically heterogeneous group of disorders including several types that are associated with sensory and variable autonomic dysfunction. These are sensory radicular neuropathy type I (HSAN I), congenital sensory neuropathy type II (HSAN II), Familial Dysautonomia (FD III), congenital insensitivity to pain with anhidrosis type IV (HSAN IV), and congenital indifference to pain associated with intellectual disability type V (HSAN V) [2]. These types are classified according to the age of onset, clinical characteristics, and the degree of both sensory and autonomic dysfunction as well as the mode of inheritance. CIPA is the second most common type of HSAN [3]. The disease is caused by a mutation in the nerve Growth Factor Receptor Tyrosine Kinase 1 (NTRK1) coded on chromosome 1q21-q22. This leads to a deficiency of the Nerve Growth Factor (NGF) dependent myelinated A $\delta$  and unmyelinated C-fibers, which clinically manifests as defective sensation to noxious stimuli and autonomic dysfunction. Absent cholinergic sympathetic innervation to sweat glands results in anhidrosis and defective thermoregulation [4]. CIPA is characterized by insensitivity to pain, anhidrosis (the inability to sweat), and intellectual disability and this condition causes repetitive injuries including oral self-mutilation; biting of fingertips; bruising, scratching, and infection of the skin [5]. Fractures, infections, growth disturbances, Joint Subluxation and Charcot joints affecting the limbs and spine are common orthopedic problems [4]. Anhidrosis predisposes to recurrent febrile episodes.

The diagnosis of NTRK1-CIPA is established in a proband with suggestive clinical findings and biallelic pathogenic variants in NTRK1 identified by molecular genetic testing. No cure is available. The treatment is supportive and is best provided by a team of specialists in pediatrics, orthopedics, dentistry, ophthalmology, and dermatology [5].

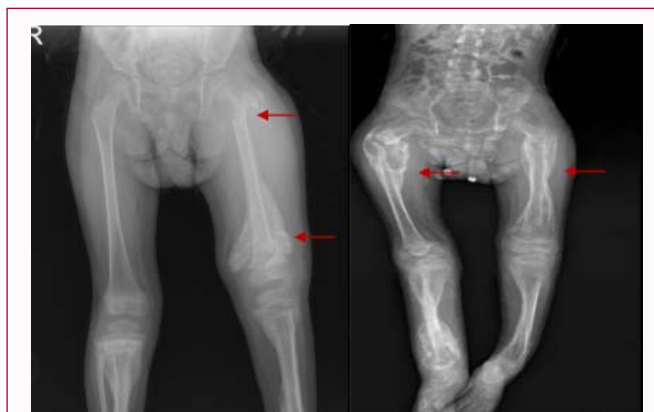
Our aim in this article, is to present a severe CIPA case presenting with bone masses and multiple fractures, also with delay in diagnosis due to an initial misdiagnosis as osteosarcoma.

## Case Presentation

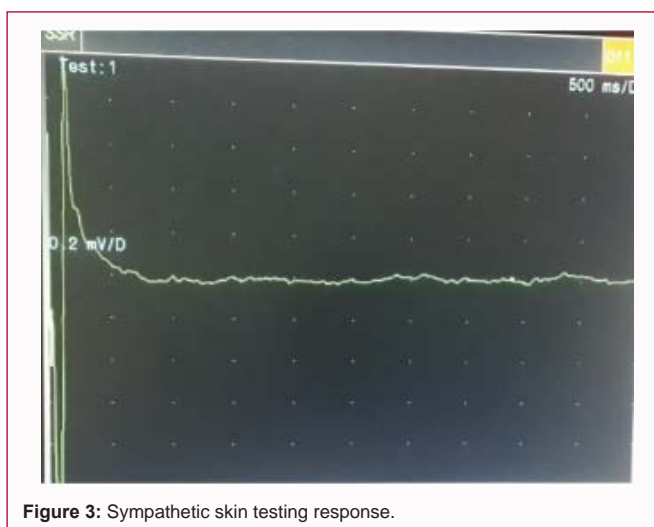
A 4-year-old female patient was consulted to the pediatric rheumatology department of Gazi University Faculty of Medicine, due to swelling in her left leg for a week. There was no known history of trauma. It was learned that the patient had a similar swelling in her left knee after falling, 6 months ago. Magnetic Resonance Imaging (MRI) revealed a solid mass of approximately 48 mm × 42 mm × 39 mm in diameters in the proximal metaphysis-diaphyseal region of the left tibia with a soft tissue component, bone marrow edema in the proximal middle diaphyseal region, and a periosteal reaction that continues up to the distal middle diaphyseal region. There was no involvement outside the lesion area in the bone scintigraphy. Since the biopsy taken from the lesion was compatible with osteosarcoma with predominant chondroblastic features, chemotherapy protocol was started. While the swelling in the left knee decreased in the first month of the treatment, a new swelling developed in the right knee. In MRI, healed mass in the left tibia was detected, but the newly developed fracture lines in the distal parts of the left tibia, fibula, and in the proximal metaphyseal area of the right tibia were seen. Since the newly developed lesion was pathologically found to be compatible with exaggerated callus formation, the two biopsy specimens, the new one and the former, were re-evaluated comparatively. So, the diagnosis of osteosarcoma was ruled out. Clinicopathologic differential diagnosis included sporadic or hereditary developmental bone diseases, melorheostosis, and progressive reactive periostitis without any definitive diagnosis (Figure 1). Thus, the patient was consulted to our department due to the suspicion of periostitis. In physical examination, there was ichthyosis on both hands. Circumference of the left thigh was 30 cm and the right thigh was 21 cm. There was no increase in temperature, redness, or tenderness in



**Figure 1:** Evident surface-marrow callus and cartilaginous tissue: an exaggerated callus reaction mimicking a chondroblastic osteosarcoma.



**Figure 2:** Fracture and callus formation in the patient's direct radiographs.



**Figure 3:** Sympathetic skin testing response.

the affected area. There was bone deformity in the old fracture area of the left ankle. When the patient was evaluated thoroughly, it was found that she could not speak, had mental retardation, and self-mutilation. Additionally, it was learned that the patient had recurrent fever episodes. Laboratory results showed that her hemoglobin was 9.1 g/dl, white blood cell count 8340/mm<sup>3</sup>, and platelet 432.000/mm<sup>3</sup>. While alkaline phosphatase and lactate dehydrogenase levels were high, other biochemistry values were normal. Anti-nuclear antibody and rheumatoid factor were negative. A fracture was detected on the left femur on X-Ray and a splint was performed (Figure 2). Pain insensitivity syndrome was considered in this patient, because she did not feel any pain despite having a fracture, had a history of recurrent fractures, was not sweating, had ichthyosis, recurrent fever episodes, and mental retardation. Nerve conduction study and needle electromyography were normal. Sympathetic skin testing response was absent (Figure 3). Whole-Exome Sequencing (WES) was performed and found a homozygous novel variant in NTRK1 gene (NM\_002529.3) (c.1998delT, p.Ile666MetfsTer6) and CIPA was diagnosed (Figure 4).

## Discussion

Congenital insensitivity to pain with anhidrosis is an extremely rare disorder which is characterized by insensitivity to painful stimuli, repeated injuries, often involuntarily self-inflicted bony destruction, recurrent febrile episodes, and intellectual disability. Sensory and sympathetic postganglionic neurons are absent in CIPA. Due to the



Figure 4: The novel variant of NTRK1 gene.



Figure 5: Physical examination findings of the patient at the last visit: A and B: Xerosis on the hands; C and D: Ulcerated lesions on the feet; E: Skeletal deformities due to the patient's previous bone fractures.

lack of neurons in both skin and skeletal system and potential trophic role of nociceptive fibers in the skeleton, bone fractures are very common [6]. Fractures in these patients heal slowly particularly in the long bones that are also susceptible to repeated trauma and infectious complications [7]. Our patient also developed recurrent skin ulcers and associated recurrent osteomyelitis during follow-up (Figure 4). Xerosis in bilateral hands and skeletal deformities due to recurrent bone fractures are also shown in Figure 4. In early childhood with excoriated skin lesions of the extremities, stomatological involvement beginning in the first year of life when the first teeth appear, bone fractures (repeated, often unnoticed, with inadequate bone union), and painless joint dislocations should make us suspicious about CIPA and should be distinguished from child abuse [8]. In the study by G. Szöke et al. 19 patients with orthopedic problems, 11 (58%) had neuropathic osteoarticular disorders of the feet and ankles, 10 (53%) of the knees, and 5 (26%) of the hips. The hands and fingers were involved in 9 (43%) and all were bilateral with mutilation of the finger tips. In four patients with elbow involvement, one Charcot joint and three dislocated joints were detected [9].

In line with published cases, our patient had joint deformities and recurrent fractures in long bones. The patient was consulted to us in terms of rheumatic disease, but the patient's current fracture and callus formations due to previous fractures in X-rays ruled out any rheumatic disease. When the findings (previous history of recurrent fever episodes, mental retardation, anhidrosis, self-mutilation, and pain insensitivity) were evaluated together, CIPA was a highly suggestive diagnosis, as genetically confirmed. The interesting point of

our case is that the patient was initially misdiagnosed as osteosarcoma and was given chemotherapy at the first presentation to our hospital.

Patients with CIPA present with healing fractures similar to osteosarcoma in imaging studies. Golshani et al. reported a CIPA case due to SCN9A mutation who had a detailed work-up to rule out neoplasm for a mass-like lesion in distal femur before genetic testing for SCN9A [10]. Callus can be defined as osteogenic or chondrogenic granulation tissue which hosts a series of tissue responses following bone fractures. Pathologic fracture is a term which refers to breaks in the bones when there is an underlying disease (i.e., bone cysts, metabolic bone disorders or primary/secondary (metastatic) tumors). Bone repairment is a complex tissue reaction depending on the extent and type of the fracture. Generally, six distinct stages may be identified in a broken bone during the healing process: (i) induction stage; hematoma formation, (ii) inflammation; characterized by neutrophil leukocytes, macrophages, and mast cells, (iii) early granulation tissue formation; initial collagen deposition and increased vascularity, (iv) soft callus; proliferation of osteoblasts and periosteal new bone formation, (v) bony (primary) callus; membranous (periosteal) and endochondral ossification, (vi) bone remodeling (secondary callus); intense osteoblast and osteoclast activity and appositional bone formation. Especially in the fourth stage, during soft callus formation, both surface and marrow callus and cartilaginous tissue may be evident. At this stage exaggerated callus reaction may mimic a chondroblastic osteosarcoma, as it caused a misconception in our case. The final stage, represents a prolonged period of bone remodeling which conversion of early stage of woven bone to more

mature lamellar bone takes place. The histopathology of callus depends on the time, microanatomical site of the fracture, and also the clinical conditions (such as stability, infection, and necrosis). Because of repetitive bone fractures and insufficient stabilization due to unawareness of the underlying disease state (CIPA), which diagnosed only after the emergence of new bone masses under chemotherapy, it was thought that this healing process could not occur properly and caused an exaggerated callus formation leading a misdiagnosis of osteosarcoma with prominent chondroblastic features in our case.

Because of the rarity of CIPA, it may be difficult to diagnose and distinguish it from other diseases, but early diagnosis is of particular importance, especially in the presence of orthopedic findings, to preserve skeletal integrity and prevent joint disorders and new fractures. Families should be warned about traumas, patients should be protected from all possible dangers in their living environment and all joints should be examined carefully in clinical visits. Since the diagnosis must first be correct in order to handle the patient correctly and to give appropriate treatment, as well as a good radiological correlation a correct pathological diagnosis is required. In this context, it should be kept in mind that the major diagnostic pathological pitfall, especially in small biopsy samples, is that the exuberant fracture callus can mimic osteosarcoma [11].

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