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Case Report

A diagnostic dilemma in an infant: a case of infantile cortical hyperostosis overlapping with chronic recurrent multifocal osteomyelitis

Dinkar Raut[1], Sagar Yamnaji Walhekar[1], Meghana M. M.[2]*, Anjini Misra[2]

[1]Yogita Paediatric Critical Care Hospital and Nursing Home, Beed, Maharashtra, India
[2]Department of Paediatrics, Government Medical College, Nagpur, Maharashtra, India

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***Correspondence:**
Dr. Meghana M. M.,
E-mail: meghanamalgis@gmail.com

ABSTRACT

Caffey's disease, first described by Caffey and Silverman in 1945 is also known as infantile cortical hyperostosis (ICH), is a condition that affects infants and is mostly self-limiting. Presenting with painful soft tissue swellings, fever and irritability, it is characterized by cortical thickening of the underlying bones. Its clinical presentation can mimic infectious osteomyelitis, leading to diagnostic challenges. We report a case of a 2-month-old male infant with multifocal bony involvement and genetic findings suggestive of chronic recurrent multifocal osteomyelitis (CRMO), but with clinical features strongly favouring Caffey disease. This case highlights the overlap between autoinflammatory bone disorders in infancy and emphasizes the importance of integrating clinical, radiological, and genetic findings to arrive at an accurate diagnosis. This case is reported to get the awareness of the paediatricians about the disease, its existence in our population, presentation, and important differential diagnoses and management.

Keywords: Infantile cortical hyperostosis, Caffey disease, Autoinflammatory bone disorders, Chronic recurrent multifocal osteomyelitis, IL1RN mutation, Periosteal reaction

INTRODUCTION

Caffey's disease, also known as ICH, can appear in two forms: a mild classical infantile form and a more severe prenatal form. The classical, milder form was first identified by Caffey and Silverman in 1945.[1] The incidence is as low as 3 per 1000 infants under six months of age worldwide, whereas reliable estimates from India remain unknown in the absence of national registries.

The classic form of Caffey's disease occurs more frequently than the prenatal type. This rare, self-limiting condition is marked by subperiosteal reactions and new bone growth, primarily affecting the diaphysis of the mandible and long bones. It typically presents in infants younger than 5 months and generally resolves on its own by the age of 2 years.[2]

It is caused by mutations in the COL1A1 gene and follows an autosomal dominant inheritance pattern. However, its clinical expression is variable due to incomplete penetrance, meaning not all individuals carrying the mutation exhibit symptoms.[2]

Early recognition of this self-limiting condition is crucial, as it can prevent unnecessary and extensive diagnostic investigations.

Patients can present with a painful swelling in the affected area and fever.[2] There is no specific laboratory test to diagnose Caffey disease, but it can present with leukocytosis, increased erythrocyte sedimentation rate

(ESR), and alkaline phosphatase (ALP), indicating an inflammatory response. In radiographs, it appears as a new bone formation, or periosteal reaction mimicking an infectious process, which should be ruled out along with other differential diagnoses as tumours, child abuse, chronic hypervitaminosis A, scurvy, malignant infantile osteopetrosis, and prolonged PGE1 infusion.[3-5]

The disease shows a good response to nonsteroidal anti-inflammatory drugs (NSAIDs).

CASE REPORT

A 2-month-old male infant presented with swelling over the left thigh and refusal to move the left lower limb, accompanied by excessive crying on passive movement of the limb for two weeks. The infant had also had mild undocumented fever and had been irritable for the past ten days. There was no history of trauma, or systemic illness. Antenatal, perinatal, and maternal histories were unremarkable, with no reported maternal infections or complications during pregnancy.

Clinical examination

On examination, the infant appeared irritable but was hemodynamically stable and not acutely ill. There was a noticeable swelling over the left thigh and groin region with restricted active and passive movement of the concerned limb. The area showed no local signs of inflammation. No other joint or systemic abnormalities were evident at initial presentation.

Laboratory investigations showed: Haemoglobin: 7.2 g/dL, total leukocyte count: 20,700/mm³, neutrophils: 62%, lymphocytes: 31%, platelets: 1.25 million/mm³ and C-reactive protein (CRP): 62 mg/l.

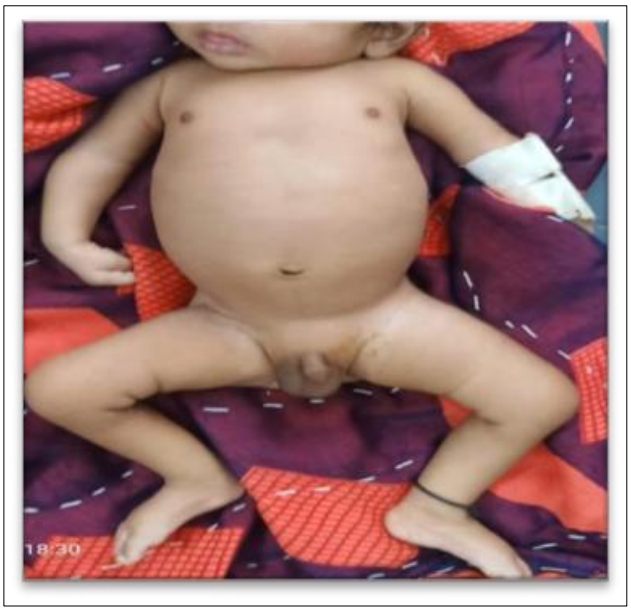


Figure 1: Swelling of the right elbow and left hip joint.

Imaging

X-ray of left thigh

Demonstrated soft tissue swelling and a solid, subperiosteal new bone formation along the diaphysis of the femur, along with cortical thickening.

Ultrasound

Revealed bulky thigh muscles without evidence of joint effusion or abscess.

MRI of pelvis and thigh

Showed diffuse soft tissue oedema and periosteal reaction along the femur with mild hip joint effusion, initially suggestive of infectious osteomyelitis.

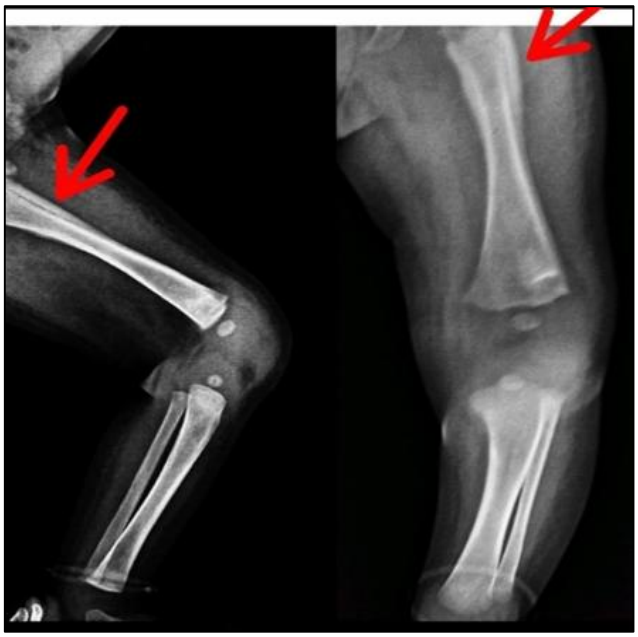


Figure 2: AP radiograph of the left thigh. Soft tissue swelling of the left thigh with underlying periosteal new bone formation and cortical thickening isolated to the diaphysis of left femur.

Based on these findings, empirical intravenous antibiotics (vancomycin, ceftriaxone, and piperacillin) were initiated alongside NSAIDs for pain control. Surgical intervention with biopsy was advised but was declined by the parents.

During the course in the hospital**,** despite antibiotic therapy, the thigh swelling persisted, although the infant's irritability reduced and limb mobility partially improved. Subsequently, new swellings developed over the right elbow and left dorsum of the hand, again with reduced movement but no systemic signs of sepsis. The child also developed multiple pustular lesions over the body. These findings indicated a poor response to antibiotics but a partial response to NSAIDs.

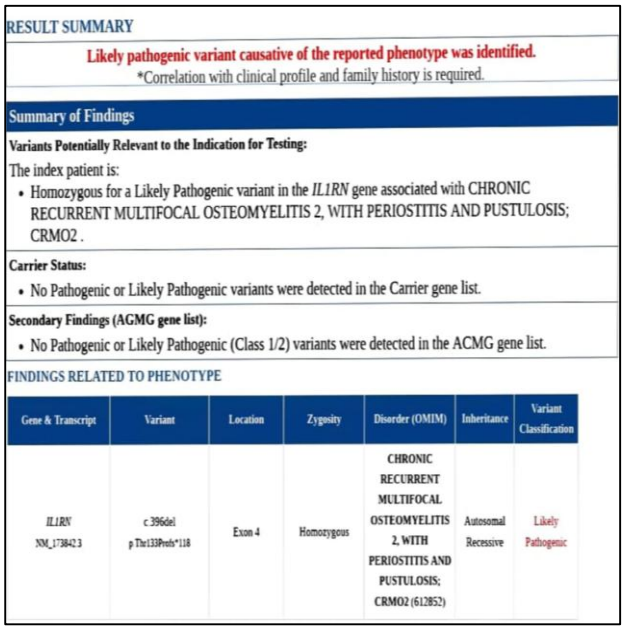
Repeat labs showed: Hemoglobin: 7.7 g/dl, platelets: 1.35 million/mm³ and lymphocytosis (60%).

Repeat X-rays demonstrated new solid periosteal reactions along the right humerus and persistent findings along the left femur, without evidence of abscess formation or lytic lesions.

Given the multifocal involvement, absence of systemic signs of infection, poor response to antibiotics, and radiological features, alternative diagnoses were considered-particularly non-infectious osteomyelitis. The differential included: ICH (Caffey disease) and CRMO.

Genetic analysis

Whole exome sequencing revealed a homozygous deletion in exon 4 of the IL1RN gene, consistent with IL-1 receptor antagonist deficiency (DIRA), a monogenic autoinflammatory condition classified under the CRMO spectrum.



RESULT SUMMARY

Likely pathogenic variant causative of the reported phenotype was identified.

*Correlation with clinical profile and family history is required.

Summary of Findings

Variants Potentially Relevant to the Indication for Testing:

The index patient is:

- Homozygous for a Likely Pathogenic variant in the *IL1RN* gene associated with CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS 2, WITH PERIOSTITIS AND PUSTULOSIS; CRMO2 .

Carrier Status:

- No Pathogenic or Likely Pathogenic variants were detected in the Carrier gene list.

Secondary Findings (AGMG gene list):

- No Pathogenic or Likely Pathogenic (Class 1/2) variants were detected in the ACMG gene list.

FINDINGS RELATED TO PHENOTYPE

Gene & Transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Variant Classification
IL1RN NM_173842.3	c.396del p.Thr133Profs*118	Exon 4	Homozygous	CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS 2, WITH PERIOSTITIS AND PUSTULOSIS; CRMO2 (612852)	Autosomal Recessive	Likely Pathogenic

Figure 3: Whole exam report of the patient.

Despite the genetic confirmation of CRMO, the early onset (2 months), pattern of bone involvement (diaphyseal cortical thickening with periosteal reaction), and clinical course (self-limiting with NSAIDs) were more consistent with Caffey Disease. It is increasingly recognized that Caffey Disease and CRMO may lie on a spectrum of autoinflammatory bone diseases, particularly in cases with IL1RN mutations.

The infant was managed conservatively with NSAIDs (Syrup Ibugesic Plus). Neither corticosteroids nor IL-1 inhibitors were used. On follow-up, the infant showed improved weight gain, reduced irritability, and progressive improvement in limb mobility.

Figure 4: Multiple pustular lesions over the body.

DISCUSSION

Caffey's disease, or ICH, remains a diagnostic challenge due to its rarity and its clinical resemblance to more common conditions such as acute osteomyelitis. First described by Caffey and Silverman, the disorder typically presents within the first five months of life with painful soft-tissue swelling, irritability, and subperiosteal new bone formation.[1] In our case, the 2-month-old male infant initially received treatment for osteomyelitis, highlighting a well-recognized diagnostic pitfall reported in earlier studies.[1,2]

In our patient, the presence of a solid periosteal reaction in multiple long bones, combined with absence of systemic toxicity and poor response to antibiotics, suggested a non-infective etiology. Such radiological features and clinical behavior are characteristic of ICH, a disease known to be self-limiting and unresponsive to antimicrobial therapy.[2]

A notable finding in our case was the homozygous deletion in exon 4 of the IL1RN gene, which is classically associated with autoinflammatory disorders such as deficiency of the IL-1 receptor antagonist (DIRA).[8] Although IL1RN mutations can produce severe systemic inflammation, our patient's phenotype was milder and more aligned with classical Caffey's disease rather than DIRA. This suggests that partial or variant IL-1 pathway disruptions may contribute to sterile osteitis presenting in infancy, supporting emerging evidence that ICH may lie on a broader spectrum of autoinflammatory bone diseases.[6]

The differential diagnosis also included CRMO, a non-infectious inflammatory bone disorder characterized by multifocal lesions and recurrent episodes of pain.[7,9] However, CRMO typically presents in late childhood or adolescence, in contrast to the early infantile onset in our case. Additionally, CRMO follows a relapsing–remitting

course rather than the rapid, self-limiting pattern observed in ICH. Key radiologic distinctions described in the literature, such as metaphyseal lesions and marrow edema in CRMO, further help differentiate it from ICH.[7,9]

Previous genetic studies have implicated COL1A1 mutations in many cases of classical Caffey's disease.[2] In contrast, the IL1RN involvement in our patient expands the possible genetic contributors to sterile infantile osteitis and strengthens hypotheses proposing a shared autoinflammatory mechanism across ICH, CRMO, and DIRA-spectrum disorders.[6,8]

Despite this overlap, treatment in our case remained conservative. The infant responded well to NSAIDs, consistent with previously published experiences that highlight the benign, spontaneously resolving nature of ICH.[1,2]

Overall, this case emphasizes the importance of differentiating Caffey's disease from infectious and other autoinflammatory bone disorders. Awareness of its clinical course, age of onset, and characteristic radiologic appearance can prevent unnecessary antibiotic exposure or invasive diagnostic procedures.

CONCLUSION

Caffey's disease, though rare, should be considered in infants presenting with limb swelling, irritability, and radiographic evidence of periosteal new bone formation, especially when unresponsive to antibiotics. Early recognition can prevent misdiagnosis as osteomyelitis and avoid unnecessary invasive treatments. While genetic overlap with conditions like CRMO may exist, clinical features and age of onset remain key differentiators.

Radiological findings combined with clinical suspicion are vital for diagnosis. Management is largely supportive, with NSAIDs providing effective symptom relief.

This case highlights the importance of clinical awareness and a multidisciplinary approach in evaluating atypical bone lesions in infants.

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