RESEARCH PAPER

Denosumab in Bisphosphonate-Refractory Polyostotic Fibrous Dysplasia in McCune–Albright Syndrome: A Case Report

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ABSTRACT

McCune–Albright syndrome (MAS) is a rare mosaic disorder characterized by polyostotic fibrous dysplasia (PFD), café-au-lait macules, and hyperfunctioning endocrinopathies. Management of skeletal disease remains challenging, particularly in patients with incomplete response to bisphosphonates.

We report a 15-year-old male with clinically diagnosed MAS presenting with extensive PFD, craniofacial involvement with optic nerve compression, multiple low-trauma fractures due to bone involvement, and markedly elevated alkaline phosphatase (ALP). Despite two years of intravenous zoledronate therapy, biochemical response was partial, with persistently elevated ALP levels.

Following transition to Denosumab, ALP declined from 1284 U/L to 294 U/L within one treatment cycle. Subsequent values showed fluctuation but remained overall lower than pre-denosumab levels. Clinically, the patient reported reduction in bone pain and no new fractures during follow-up.

This case highlights denosumab as a potential therapeutic option in bisphosphonate-refractory MAS associated PFD. However, variability in biochemical response and limited long-term safety data warrant cautious use and close monitoring.

Keywords: McCune–Albright syndrome, Polyostotic fibrous dysplasia, Denosumab, Bisphosphonate-refractory, Case report.

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Introduction

McCune–Albright syndrome (MAS) is a rare, sporadic disorder caused by postzygotic activating mutations in the GNAS gene, leading to constitutive activation of Gsα signaling and increased cAMP production.[1]. Clinical manifestations are heterogeneous due to mosaic distribution of affected cells [2].The classic triad of McCune-Albright syndrome (MAS) includes polyostotic fibrous dysplasia (PFD), hyperpigmented café-au-lait macules with irregular (i.e., “coast of Maine”) borders, and endocrinopathies [3]. While many patients with MAS have all three components, it is not uncommon to see patients who do not have all three features, which may delay their diagnosis [4].

The skeletal component—polyostotic fibrous dysplasia (PFD)—is often the most disabling feature, resulting in fractures, deformities, and elevated bone turnover markers such as alkaline phosphatase (ALP) [5,6]. Bisphosphonates are commonly used but frequently produce incomplete biochemical responses. [7].Denosumab, a monoclonal antibody targeting RANKL, has emerged as a potential alternative by directly inhibiting osteoclastogenesis. However, evidence remains limited, particularly in pediatric MAS.[6,8] We present a case of MAS with severe PFD demonstrating suboptimal response to zoledronate and subsequent biochemical and clinical improvement following denosumab.

Case Presentation

Patient Background and Antenatal/Perinatal History

A 15-year-old male presented with multiple low-trauma fractures, craniofacial involvement complicated by hearing improvement and optic

nerve compression requiring decompressive surgery.

There was no history suggestive of precocious puberty or other endocrinopathies. On physical examination, his height was 158 cm (10–25th centile). Weight - 52kg (25-50th centile), BMI-21kg/m2. Sexual maturity rating $A^{+}P^{5}$ bilateral testicular volume 20ml. He had facial asymmetry, kyphoscoliosis, limb length discrepancy. Multiple cafe-au-lait macules (five in number) were noted over the body, which were irregular in outline and did not cross the midline.

Investigations and Serial Biochemical Monitoring

Serial biochemical monitoring included ALP, calcium, phosphorus, vitamin D, PTH, thyroid function, and gonadal hormones (Table 1).Baseline testosterone (692.6 ng/dL), consistent with late pubertal physiology. Diagnosis of MAS was made based on clinical and radiological features, in line with FD/MAS consortium criteria. Genetic confirmation was not performed due to limitations in mosaic mutation detection and financial issues.

Table 1: Serial Biochemical Parameters with Treatment Milestones

Date	Treatment Phase	ALP (U/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Vit D (ng/mL)	Notes
Aug 2022	Baseline	2505	9.9	4.0	15.2	Started zolendronate
Oct 2023	Zoledronate	1837	—	4.3	—	Partial response
Apr 2024	Zoledronate	1475	9.9	3.9	19.6	—
Dec 2024	**Pre-denosumab**	**1284**	**—**	**3.4**	**—**	**Switch therapy**
Jan 2025	Post-denosumab	294	8.46	3.18	42.1	Rapid decline
Aug 2025	Follow-up	1399	—	—	—	Fluctuation
Sep 2025	Follow-up	1021	—	—	—	Improving
Dec 2025	Follow-up	386	—	—	—	Improving

Mar 2026	Follow-up	820	—	—	—	Improving

Zoledronate dose: 4 mg intravenous - 2 doses were given once yearly
Denosumab dose: 60mg subcutaneous was administered every 2-3 months, with a total of 5 doses during follow up.

Treatment and Outcome

The patient was initially treated with intravenous zoledronate from August 2022 to December 2024, during which a partial biochemical response was observed, with serum alkaline phosphatase (ALP) decreasing from 2505 U/L to 1284 U/L. In view of the suboptimal response, therapy was transitioned to denosumab in December 2024 (dose and dosing interval to be specified). Following initiation, a marked decline in ALP to 294 U/L was observed after a single treatment cycle. Subsequent measurements demonstrated fluctuations in ALP levels, although values remained overall lower compared to the predenosumab phase. Clinically, the patient reported improvement in bone pain and did not experience any new fractures but there was no improvement in vision during the follow-up period. Serum calcium levels remained stable with appropriate supplementation. No episodes of hypocalcaemia or rebound hypercalcaemia were documented during 15 months of follow-up

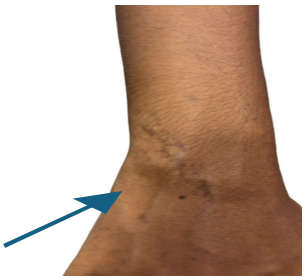

Figure 1. Plain radiograph showing ground-glass appearance involving the distal femur, consistent with fibrous dysplasia

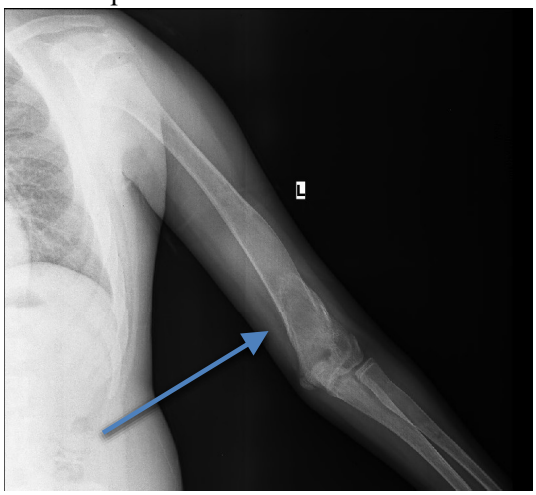

Figure 2. CT skull demonstrating diffuse craniofacial fibrous dysplasia with narrowing of the optic canal (arrows)

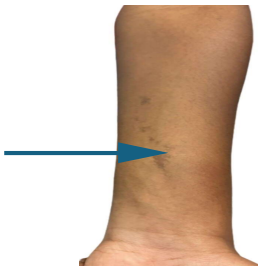

Figure 3. Clinical images showing irregular cafe-au-lait macule respecting the midline

Discussion

This present case illustrates the clinical heterogeneity and therapeutic challenges of MAS-associated PFD, including the variability of clinical manifestations and the therapeutic challenges associated with managing polyostotic fibrous dysplasia (PFD). The diagnosis in this patient was based on characteristic clinical and radiological features, including extensive skeletal involvement and café-au-lait macules, in keeping with established FD/MAS consortium criteria. Although genetic confirmation was not performed, this reflects real-world limitations related to the mosaic nature of GNAS mutations and the low sensitivity of peripheral testing.[4].

A notable feature of this case is the absence of classical endocrine hyperfunction. MAS is commonly associated with gonadotropin-independent precocious puberty, particularly in females; however, endocrine manifestations in males are less frequent and more heterogeneous.[2]. In this patient, pubertal development occurred within the expected chronological window, and testosterone levels were consistent with late pubertal physiology. Importantly, gonadotropin levels were not suppressed, arguing against peripheral precocious puberty. This patient lacked the classical endocrine manifestations typically described in MAS, and emphasize the importance of interpreting hormonal data in the context of pubertal stage to avoid misclassification.

Fibrous dysplasia is the most functionally disabling manifestation of MAS, and elevated ALP has been established as the most reliable and widely used biomarker of disease activity and treatment response [6,9]. In our patient, a baseline ALP of 2505 U/L reflected extensive disease .In this case, prolonged treatment with zoledronate resulted in only partial biochemical improvement, with persistently elevated ALP levels,

consistent with previous reports demonstrating variable and often incomplete responses to bisphosphonates in MAS-associated PFD. [7]. Denosumab offers a mechanistically distinct therapeutic approach by directly inhibiting RANKL-mediated osteoclast activation.[5]. Following initiaton of denosumab, this patient demonstrated a rapid and marked reduction in ALP, indicating effective suppression of bone turnover. The pattern of biochemical responses observed in our patient after initiating denosumab is consistent with those reported in the literature for patients with FD who are resistant to bisphosphonates[8]. In addition to biochemical changes, the patient reported improvement in bone pain and did not experience new fractures during follow-up, suggesting a clinically meaningful benefit.This symptom relief has been similarly demonstrated in various studies to be associated with decreased osteoclast activity in patients with FD [9] Nevertheless, objective measures of functional improvement and radiological response were not available, limiting assessment of the full therapeutic impact.

Safety considerations are particularly important when using denosumab in paediatric populations. While no episodes of hypocalcaemia or rebound hypercalcaemia were observed during 15 months follow-up period in this case, these complications are well described and warrant careful monitoring. The potential for rebound increases in bone turnover following discontinuation also remains a concern and underscores the need for clearly defined treatment strategies[10]. The fluctuating ALP values for our patient after the initation of denosumab may be primarily related to the dosing interval or due to partial rebound effects between doses, underscoring the importance of regularly scheduled dosing and monitoring .

The limitations of this case include lack of genetic confirmation of MAS and absence of serial imaging to assess structural response. Additional limitations include reliance on ALP as a surrogate marker of disease activity, absence of standardised pain assessment, and the inherent limitations of a single-case observation.

Serial ALP measurements were useful in monitoring treatment response in this patient as a practical, accessible, and informative tool to guide therapeutic decisions in MAS-associated PFD. It supports the growing body of evidence that denosumab represents potential therapeutic option in patients with inadequate response to bisphosphonates, and may warrant earlier

consideration in the management algorithm for severe paediatric PFD. Larger prospective studies are required to define optimal dosing strategies, duration of therapy, and long-term safety outcomes in MAS.

Conclusion

Denosumab may provide biochemical and clinical benefit in patients with MAS-associated PFD who show suboptimal response to bisphosphonates. However, variability in response and limited long-term safety data necessitate cautious use and further studies.

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