

Multimodal Biological Augmentation with Umbilical Cord Mesenchymal Stem Cell Secretome, Recombinant Human Bone Morphogenetic Protein-2, and Allogeneic Umbilical Cord Mesenchymal Stem Cells in Neurofibromatosis Type 1-Confirmed Congenital Pseudarthrosis of the Distal Tibia and Fibula: A Case Report with Mechanistic Scoping Review

Luh Gede Djatu Anggitadewi^{1,2}, Oen Sindrawati², Komang Agung Irianto^{1,2}, Tri Wahyu Martanto¹

Learning Point of the Article:

Quadruple biological augmentation combining UC-MSC secretome (two-stage delivery), allogeneic UC-MSC, rhBMP-2, and synthetic HA scaffold simultaneously targets the three convergent pathological pathways of NF1-associated CPT and is clinically feasible.

Abstract

Introduction: Congenital pseudarthrosis of the tibia (CPT) associated with neurofibromatosis type 1 (NF1) is characterized by convergent dysregulation of three molecular pathways – transforming growth factor-beta/Smad-driven fibrogenesis, RAS-MEK-ERK hyperactivation, and Wnt/ β -catenin blockade – none of which is addressed by conventional surgical fixation alone. This case explores the clinical feasibility of a multimodal biological protocol targeting all three pathways simultaneously.

Case Report: A 6-year-old male with histopathologically confirmed NF1-associated Crawford type IV CPT of the distal tibia and concurrent distal fibular pseudarthrosis underwent radical hamartoma excision combined with quadruple biological augmentation: Allogeneic umbilical cord mesenchymal stem cells (UC-MSC) (20 million cells), UC-MSC conditioned medium (secretome; first injection intraoperatively post-graft), recombinant human bone morphogenetic protein-2 (rhBMP-2) (Novosys), and synthetic hydroxyapatite scaffold (Bongros), stabilized with an Ilizarov trans-ankle external fixator. A second secretome injection (1.4 mL, fluoroscopy-guided) was administered percutaneously at 8 months, targeting the distal tibial union site during frame removal.

Conclusion: Tibial callus measured 9.88 mm at 6 months (equalling diaphyseal width) with no graft resorption. At 8 months, tibial bridging callus was sufficient to permit Ilizarov frame removal without refracture. The distal tibial pseudarthrosis was stabilized with retained K-wires; the fibula received no internal fixation and showed no ongoing healing. No infection or hardware complication occurred. This case is, to our knowledge, the first to describe this quadruple augmentation protocol and a two-stage secretome delivery strategy in CPT, providing a hypothesis-generating proof of concept for future translational investigation.

Keywords: Congenital pseudarthrosis tibia, neurofibromatosis type 1, mesenchymal stem cell secretome, recombinant bone morphogenetic protein-2, Ilizarov.

Author's Photo Gallery



Dr. Luh Gede Djatu Anggitadewi



Dr. Oen Sindrawati



Dr. Komang Agung Irianto



Dr. Tri Wahyu Martanto

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¹Department of Orthopaedics and Traumatology, Dr. Soetomo General Academic Hospital/Faculty of Medicine, Airlangga University, Surabaya, Indonesia,
²Department of Orthopaedics and Traumatology, Surabaya Orthopaedics and Traumatology Hospital, Surabaya, Indonesia.

Address of Correspondence:

Dr. Luh Gede Djatu Anggitadewi,
Surabaya Orthopaedic and Traumatology Hospital, Surabaya, Indonesia.
E-mail: dr_anggitadewi@yahoo.co.id

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Introduction

Congenital pseudarthrosis of the tibia (CPT) is one of the most biologically refractory conditions in pediatric orthopedics, affecting approximately 1 in 140,000–190,000 live births [1]. In neurofibromatosis type 1 (NF1)-associated cases – which account for 40–80% of all CPT – three pathological pathways converge simultaneously: Transforming growth factor-beta (TGF- β 1)-driven fibrogenesis (“racing fibrosis”) via Smad2/3 and RhoA-MRTF-SRF; RAS-MEK-ERK hyperactivation secondary to NF1 biallelic loss in skeletal stem/progenitor cells (SSPCs), impairing osteoblastogenesis and elevating RANKL/OPG; and Wnt/ β -catenin blockade via osteocyte-derived sclerostin overexpression [2,3]. Standard surgical fixation with an intramedullary rod or Ilizarov external fixation achieves primary union in 67–84% of cases, but refracture rates remain 22–48%, underscoring the persistent biological unmet need [4].

Umbilical cord mesenchymal stem cells (UC-MSC) secretome – comprising conditioned medium (CM), extracellular vesicles, and soluble factors – theoretically engages all three pathways simultaneously: anti-fibrotic via hepatocyte growth factor (HGF), prostaglandin E2 (PGE2), and exosomal miR-21-5p (TGF- β R suppression); pro-osteogenic via Wnt ligands, insulin-like growth factor 1, and bone morphogenetic protein (BMP-2/7) (Wnt/ β -catenin rescue); and immunomodulatory via M1→M2 macrophage polarization [5,6]. Kurniawan et al. reported the only published clinical series of UC-MSC + secretome in CPT (n = 6; primary union 83%; final union 100% at 29 months) [7]. No published case has combined secretome

with recombinant human BMP-2 (rhBMP-2), allogeneic UC-MSC whole cells, and a synthetic HA scaffold simultaneously, nor described a two-stage percutaneous secretome booster protocol.

We report the first case of this quadruple biological augmentation strategy with two-stage secretome delivery in NF1-confirmed Crawford type IV CPT of the distal tibia and concurrent fibular pseudarthrosis.

Case Report

Patient demographics and pre-operative assessment

A 6-year-old male (age at surgery: 6 years 2 months) presented with a right distal tibial CPT and concurrent distal fibular pseudarthrosis (Crawford type IV), with no prior surgical history. Clinical examination revealed severe anterior bowing of the right distal tibia, inability to bear full weight independently, and restricted ankle range of motion secondary to the angular deformity. Limb length discrepancy was evident on standing anteroposterior (AP) whole-leg radiograph (Fig. 1a). Neurovascular status was intact distally. NF1 status was confirmed histopathologically from the hamartoma excision specimen: spindle cells with thin wavy nuclei, bland chromatin, and growth pushing host bone – consistent with neurofibromatosis, absent of atypia or anaplastic changes. Thoracolumbar radiographs showed no dystrophic scoliosis.

Pre-operative radiographs (Fig. 1b and c) demonstrated Crawford type IV CPT: Atrophic pseudarthrosis of the distal tibia with severe anterior bowing, sclerotic tapered bone ends,

and concurrent pseudarthrosis of the distal fibula. The dual pseudarthrosis configuration eliminated the natural splinting role of an intact fibula, representing a particularly challenging biological and biomechanical environment. From a prognostic standpoint, NF1-associated Crawford type IV CPT with concurrent fibular pseudarthrosis carries the highest reported risk of refracture and non-union among all CPT subtypes [4,8].

Surgical procedure (November 19, 2025)

Under general anesthesia (operative duration: 3 h 15 min; blood loss: 50 mL; no transfusion), the following steps were performed sequentially:

(1) Longitudinal incision over the distal

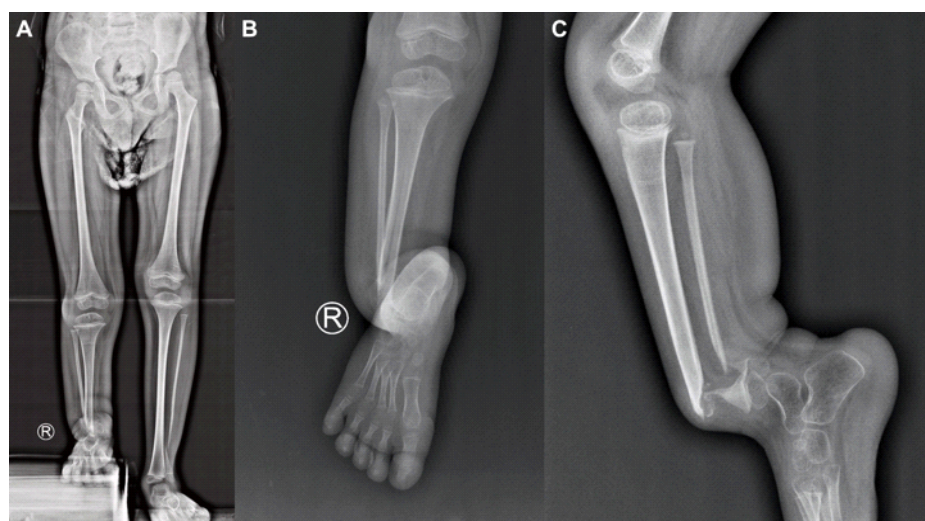


Figure 1: Pre-operative radiographs: (a) standing anteroposterior whole-leg radiograph demonstrating right limb length discrepancy with shortening and valgus deformity at the level of the pseudarthrosis. The left cruris also showed distal fibula pseudarthrosis. (b) Anteroposterior radiograph of the right cruris. (c) Lateral radiographs of the right cruris. Crawford type IV congenital pseudarthrosis of the tibia: Atrophic pseudarthrosis of the distal tibia with severe anterior bowing, sclerotic tapered bone ends, and concurrent pseudarthrosis of the distal fibula – no callus formation.

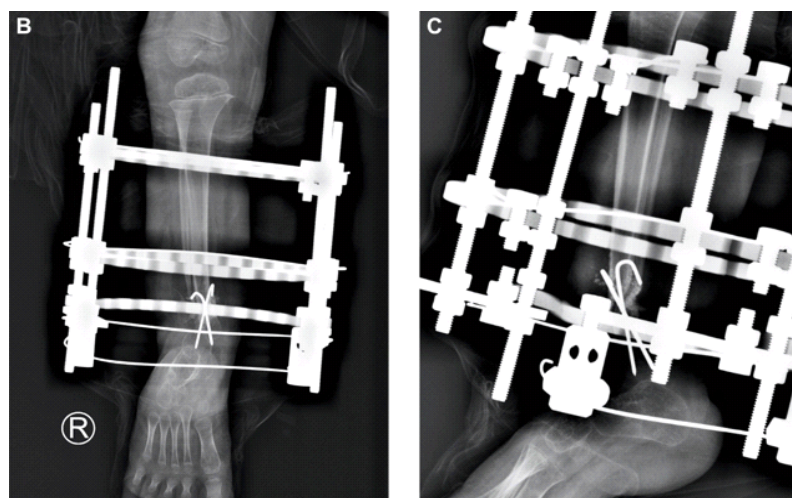


Figure 2: Post-operative radiographs: (a) Anteroposterior cruris showing Ilizarov construct with tibial rings, crossed K-wires at pseudarthrosis site, and threaded rods; (b) foot axial view showing trans-ankle foot ring configuration – hardware in position; no acute complication.

tibia with exposure of both tibial and fibular pseudarthrosis sites. (2) Radical excision of hamartomatous fibrous tissue until healthy bleeding bone ends were confirmed at both sites; the specimen was sent for histopathology (result: consistent with NF, as above). (3) Cross-pinning with K-wires at the distal tibial pseudarthrosis site only – no internal fixation at the fibular site. (4) Biological augmentation in sequence: Bongros (synthetic hydroxyapatite; osteoconductive scaffold) + Novosys (rhBMP-2; SMAD1/5/8-driven osteoblast differentiation, partially counteracting sclerostin-mediated Wnt blockade) + allogeneic UC-MSC whole cells (20 million cells; multipotent osteoprogenitor, sustained paracrine source, avoids autologous quality limitations in NF1-CPT [9]) packed into the defect, followed by UC-MSC CM (secretome; first injection) delivered as the final biological layer. (5) Application of Ilizarov external fixator with trans-ankle configuration: two tibial rings with half-pins + foot ring with calcaneal pins, enabling progressive compression at the tibial pseudarthrosis site. Post-operative management included antibiotic prophylaxis per institutional guideline and calcium/Vitamin D supplementation.

The delivery sequence (graft first, UC-MSC second, and secretome last) was chosen to: (a) establish a structural and osteoinductive scaffold before paracrine signaling; and (b) allow the secretome to function as a biological sealant, maximizing its concentration at the graft-bone interface.

Post-operative follow-up

At 9 days, the patient was ambulatory with frame support (Fig. 2); pain had resolved (FLACC score 1, subsequently 0). At 6 months (May 16, 2026), radiological assessment demonstrated tibial callus formation with a measured AP diameter of 9.88 mm

on lateral projection – equalling the width of the tibial diaphysis on the sagittal view – with no graft resorption (Fig. 3). The radiologist's report confirmed no osteomyelitis and hardware in position; the distal tibiofibular pseudarthrosis was noted to show ongoing healing.

At 8 months (July 19, 2026), sufficient tibial bridging callus was confirmed clinically and radiologically to permit Ilizarov frame removal under general anesthesia (Fig. 4). At the time of removal, a second UC-MSC secretome injection (1.4 mL, percutaneous, fluoroscopy-guided) was delivered to the distal tibial union site to provide continued paracrine stimulation during the cortical remodeling phase. K-wires were retained at the distal tibial site.

Post-removal radiographs demonstrated bridging callus at the tibial site with cortical continuity forming on both AP and lateral projections; anterior bowing was appreciably reduced; the fibular site showed ongoing healing without internal fixation or bridging. No refracture occurred. Pain score was 0 (NRS) at 8-month visit; the patient ambulated independently within the frame period. A patellofemoral-tibial brace was planned for post-removal rehabilitation. Summary of outcomes (Table 1).

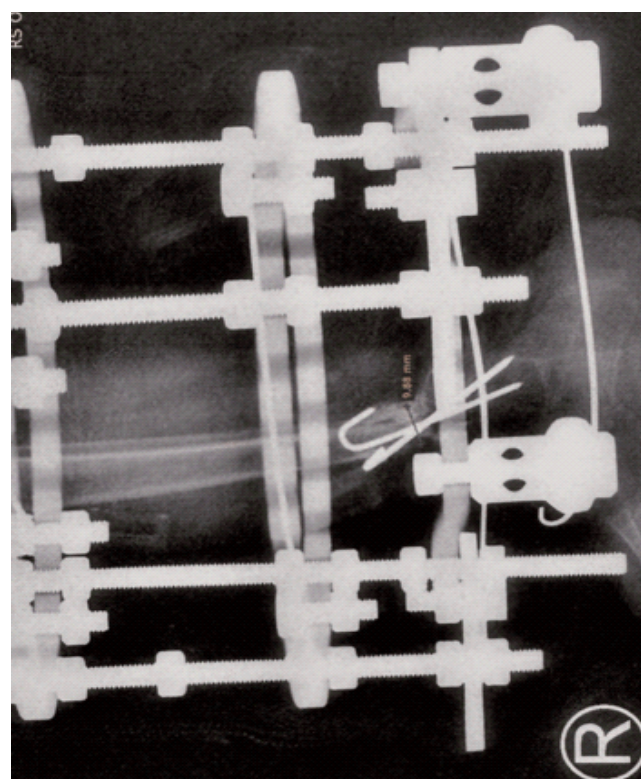


Figure 3: Lateral radiograph at 6 months (May 16, 2026). Digital measurement: tibial callus anteroposterior diameter 9.88 mm. Ilizarov frame intact. No graft resorption.

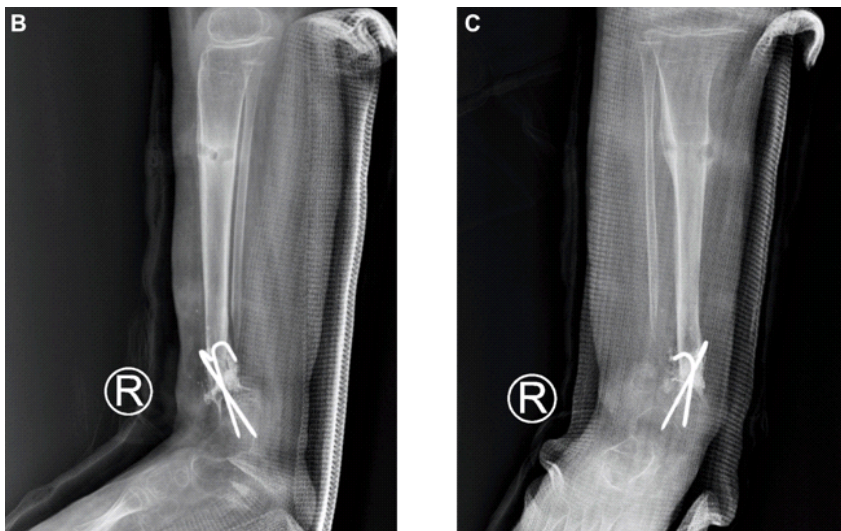


Figure 4: Post-frame-removal radiographs at 8 months (July 19, 2026): (a) Anteroposterior and (b) lateral projections. Bridging callus at tibial pseudarthrosis site; cortical continuity forming; anterior bowing improved. K-wires retained at distal tibial site. Fibular site: ongoing healing, no internal fixation. No refracture.

Discussion

This case presents three interconnected novelties in managing NF1-associated CPT. First, it is the first reported application of quadruple biological augmentation – combining UC-MSc secretome, allogeneic UC-MSc, rhBMP-2, and a synthetic HA scaffold simultaneously – in CPT. Kurniawan et al. [7], the only prior clinical series of UC-MSc secretome in CPT, used UC-MSc + CM alone with locking plate fixation, achieving 83% primary union and 100% final union at a mean of 29 months (n = 6). The present protocol augments this approach with rhBMP-2 and a superior biomechanical construct (Ilizarov with dynamic compression), and adds a novel two-stage secretome delivery strategy.

Second, the two-stage secretome delivery – intraoperative (post-graft, as final biological layer) plus percutaneous fluoroscopy-guided booster at 8 months – has not been previously described in CPT. The rationale for the booster is mechanistically grounded: At 8 months, the maturing callus may benefit from renewed anti-fibrotic and pro-osteogenic paracrine stimulation to accelerate cortical remodeling and reduce the risk of delayed union at the tibial site.

Third, this is the first mechanistically annotated case systematically mapping each biological component to a specific CPT pathway. The secretome's anti-fibrotic effect (TGF- β R suppression via HGF, PGE2, and exosomal miR-21-5p [5,6]) directly targets the racing fibrosis driven by NF1-deficient SSPCs in the residual periosteum – the mechanism that is not addressed by fixation, graft, or BMP-2 alone. The allogeneic UC-

MSc source is preferred over autologous MSC in NF1-CPT patients: Dilogio et al. [9] demonstrated that autologous CPT-derived MSC quality is intrinsically compromised, likely secondary to NF1 haploinsufficiency in the marrow compartment. rhBMP-2 bypasses the sclerostin-mediated Wnt blockade via the SMAD1/5/8 axis [10], whereas Bongros provides the osteoconductive matrix through which both the secretome and BMP-2 signal. The Ilizarov frame provided dynamic compression at the tibial pseudarthrosis site, enabling piezoelectric and mechanotransduction stimulation of callus [4]; trans-ankle fixation immobilized the distal fibular site, compensating for the absence of natural fibular splinting in this dual-pseudarthrosis configuration.

The differential union response between tibia (bridging callus at 8 months) and fibula (ongoing healing) is attributable to multiple factors: (1) the tibial site received K-wire fixation providing mechanical stability, whereas the fibular site had no internal fixation; (2) a smaller fibular bone cross-section and lower BMP-2 delivery density at the fibular site; and (3) possible differential NF1 haploinsufficiency expression in fibular SSPCs. Future protocols should consider fibular-specific biological delivery.

Limitations include the single-case design, absence of a control arm, short follow-up (8 months insufficient to confirm durable union or assess long-term refracture risk), and undocumented secretome preparation parameters (CM volume, EV concentration, and passage number). These gaps are shared with Kurniawan et al. [7] and define the evidence requirements

Table 1: Summary of clinical and radiological outcomes at 6 and 8 months postoperatively

Outcome	Tibia	Fibula
6-month callus	9.88 mm AP diameter; no graft resorption	Not yet bridged
8-month frame removal	Bridging callus; cortical continuity forming; alignment improved	Ongoing healing; no internal fixation
Refracture	None	None
Infection/hardware complication	None	None
Second secretome injection	1.4 mL CM; percutaneous under fluoroscopy (Jul 19, 2026)	Not performed
Functional status	Frame-assisted ambulation; NRS 0 at 8 months; PTB brace planned	—

PTB: Patellofemoral-tibial brace, AP: Anteroposterior, CM: Conditioned medium

for future controlled trials. The mechanistic rationale for UC-MSC secretome in CPT triple-axis pathobiology has been reported by Kurniawan et al. [7].

Conclusion

Quadruple biological augmentation with UC-MSC secretome (two-stage delivery), allogeneic UC-MSC, rhBMP-2, and synthetic HA scaffold is clinically feasible in NF1-confirmed Crawford type IV CPT, with preliminary evidence of tibial bridging callus at 8 months without refracture. This protocol simultaneously targets the three convergent pathological pathways of NF1-associated CPT and introduces a novel two-stage secretome delivery strategy. Prospective controlled

studies with standardized secretome dosimetry and longer follow-up are required to confirm efficacy.

Clinical Message

In NF1-associated Crawford type IV CPT, combining UC-MSC conditioned medium (secretome), allogeneic UC-MSC, rhBMP-2, and synthetic HA scaffold as quadruple biological augmentation – with secretome delivered as the final layer after graft packing and repeated percutaneously at frame removal – is a novel, mechanistically-informed strategy that may overcome the biological limitations of fixation alone. This two-stage secretome delivery approach targets the unique triple-pathway convergence of NF1-associated CPT and warrants investigation in prospective multicentre trials.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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