

# EXTENSIVE BILATERAL MANDIBULAR PSEUDOTUMOR IN A BOY WITH TYPE 3 VON WILLEBRAND DISEASE (VWD) TREATED WITH PLASMA DERIVED VWF/FVIII CONCENTRATE: DIAGNOSIS, TREATMENT AND OUTCOME

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**Background:** Pseudotumor is a rare and potentially serious complication of hemophilia which has been exceptionally described in VWD. Pseudotumor affects bones and soft tissues, being much more frequent in femur, pelvis and small bones. Type 3 VWD is an uncommon autosomal recessive bleeding disorder with severe deficiency of VW factor and low levels of Factor VIII. VW factor is best known for its role in haemostasis; however in recent years other functions of VWF have been identified, indicating that this protein is involved in multiple processes. The pathogenesis and management of pseudotumor in VWD remain fields of debate and research.

**Aims:** To describe the clinical features, imaging findings, management and outcome of a boy with type 3 VWD with bilateral mandibular pseudotumor treated with plasma-derived VWF/FVIII concentrate (*Humate-P®*).

**Methods:** Case report. Complete blood cell count, blood smear inspection, activated partial thromboplastin time (APTT), prothrombin time, FVIII:C, VWF:Ag (LIA and ELISA) and VWF:RCo (aggregometry) were tested. Multiplex ligation-dependent probe amplification (MLPA) for large deletions detection was performed. DNA sample was sent to ThromboGenomics for next generation sequencing of the VWF gene.

**Results:** A 6 year-old Peruvian boy was referred to our center with a diagnosis of severe hemophilia A performed at 13 months of age. He had had severe epistaxis, gingivorragia, easy bruising and anemia since the first year of age, which was treated with fresh frozen plasma and blood transfusions in his native country. He has never had hemarthrosis. A laboratory study was performed in our hospital supporting the diagnosis of type 3 VWD (Table 1). The acute episodes were treated with plasma-derived VWF/FVIII concentrate with good clinical response.

**Table 1. Laboratory data**

	Platelet count (x10 <sup>9</sup> L <sup>-1</sup> )	APTT (sec)	VIII:C (IU/dL)	VWF:Ag (IU/dL)	VWF:RCo (IU/dL)	Blood group
Propositus	298	80	4	< 1	< 6	O
Father	306	37	88	45	31	A
Mother	Not available					
Reference range	150-300	32 - 45	50 - 150	O group: 38-116 Non-O group:56-157	O group: 37-110 Non-O group:54-148	----

MLPA showed no large deletion.

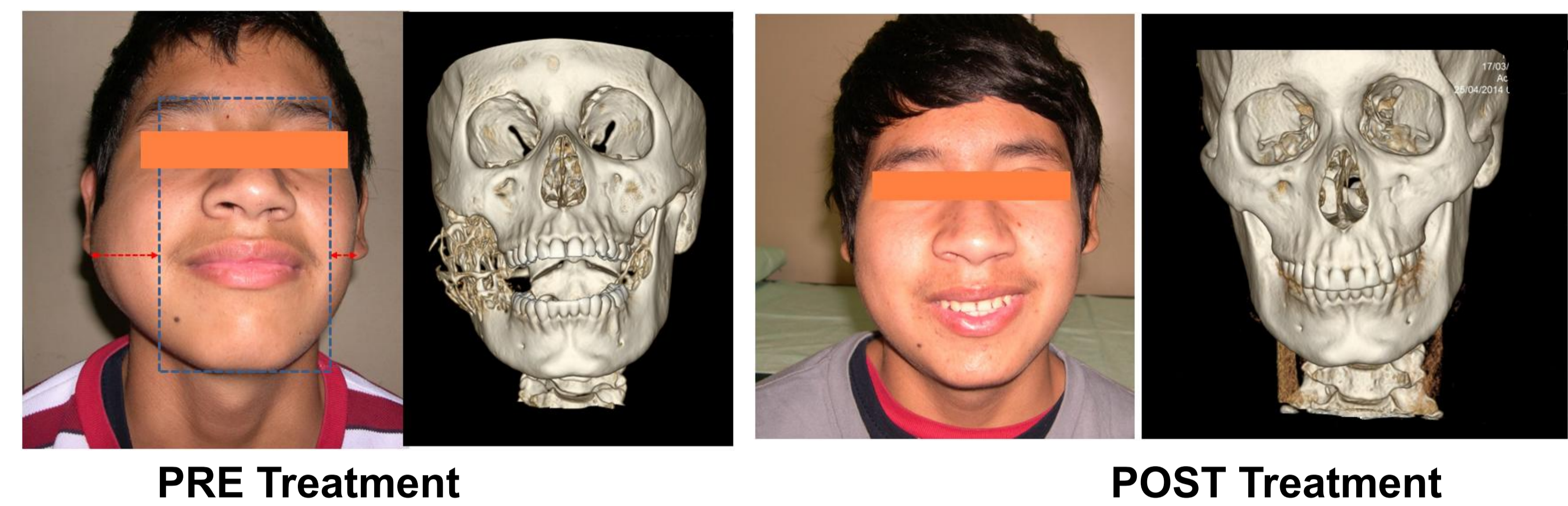
Next generation sequencing detected a homozygous insertion of two nucleotides, c.7664-7665insAG, in exon 45 of the VWF gene. This variant leads to a frameshift that causes a premature stop codon at amino acid 2565;p.(Cys2557SerfsTer8).

At 13 years of age he developed, over the course of 1 month progressive painless slow-growing tumefactions in the angles of both mandibles (Figure 1). Previous trauma was denied.

A CT scan detected bilateral lesions of both mandibles (Figure 2). A surgery biopsy was performed. No cancer was detected. Data shown in Figures 3 and 4.

Plasma-derived VWF/FVIII concentrate (*Humate-P®*) along with tranexamic acid (10 mg/kg every 6 hr) were given pre- and post- surgery followed by prophylaxis with VWF/FVIII concentrate 50 IU VWF:RCo/kg twice a week for 50 months.

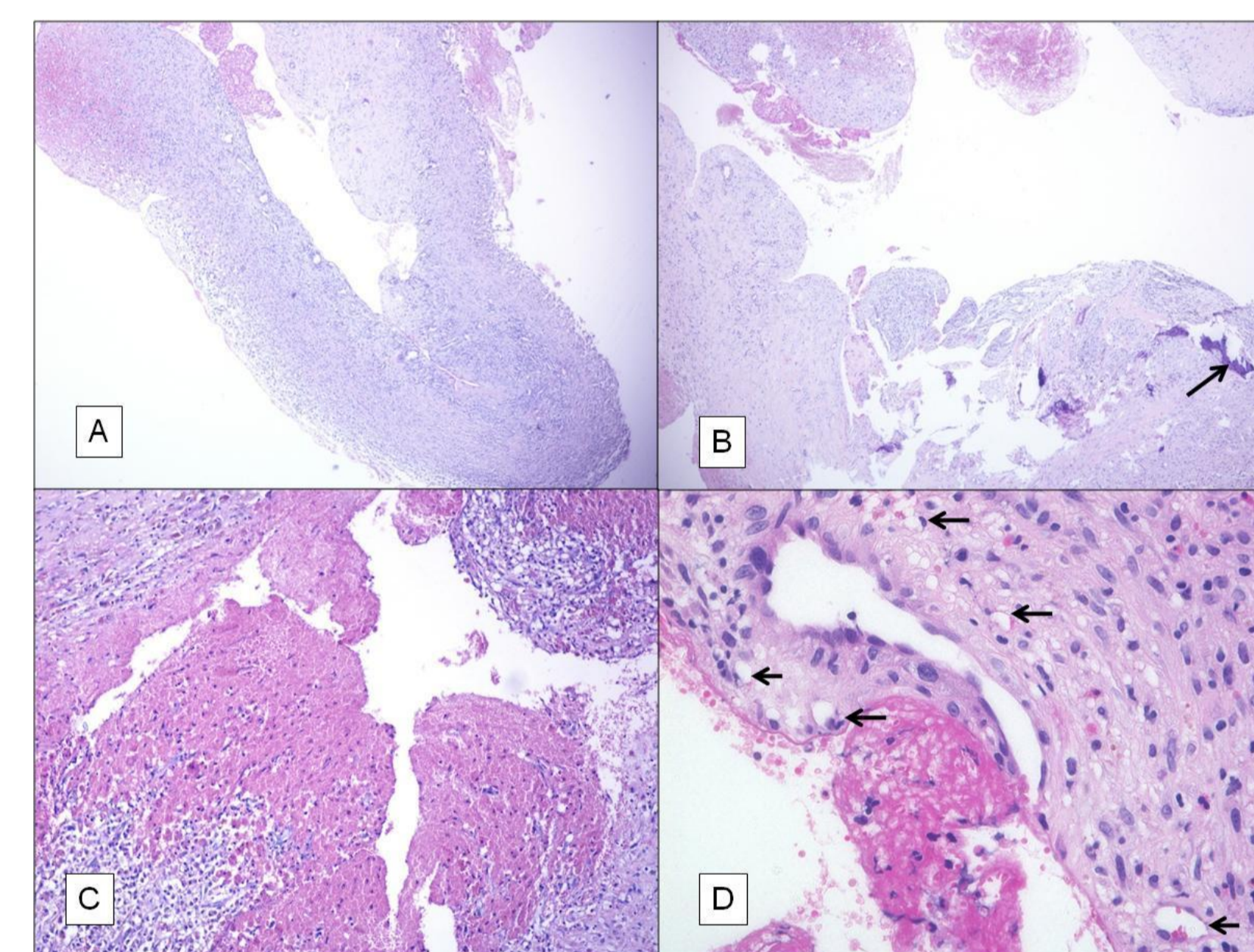
## Clinical features and imaging findings pre- and post plasma-derived VWF/FVIII concentrate



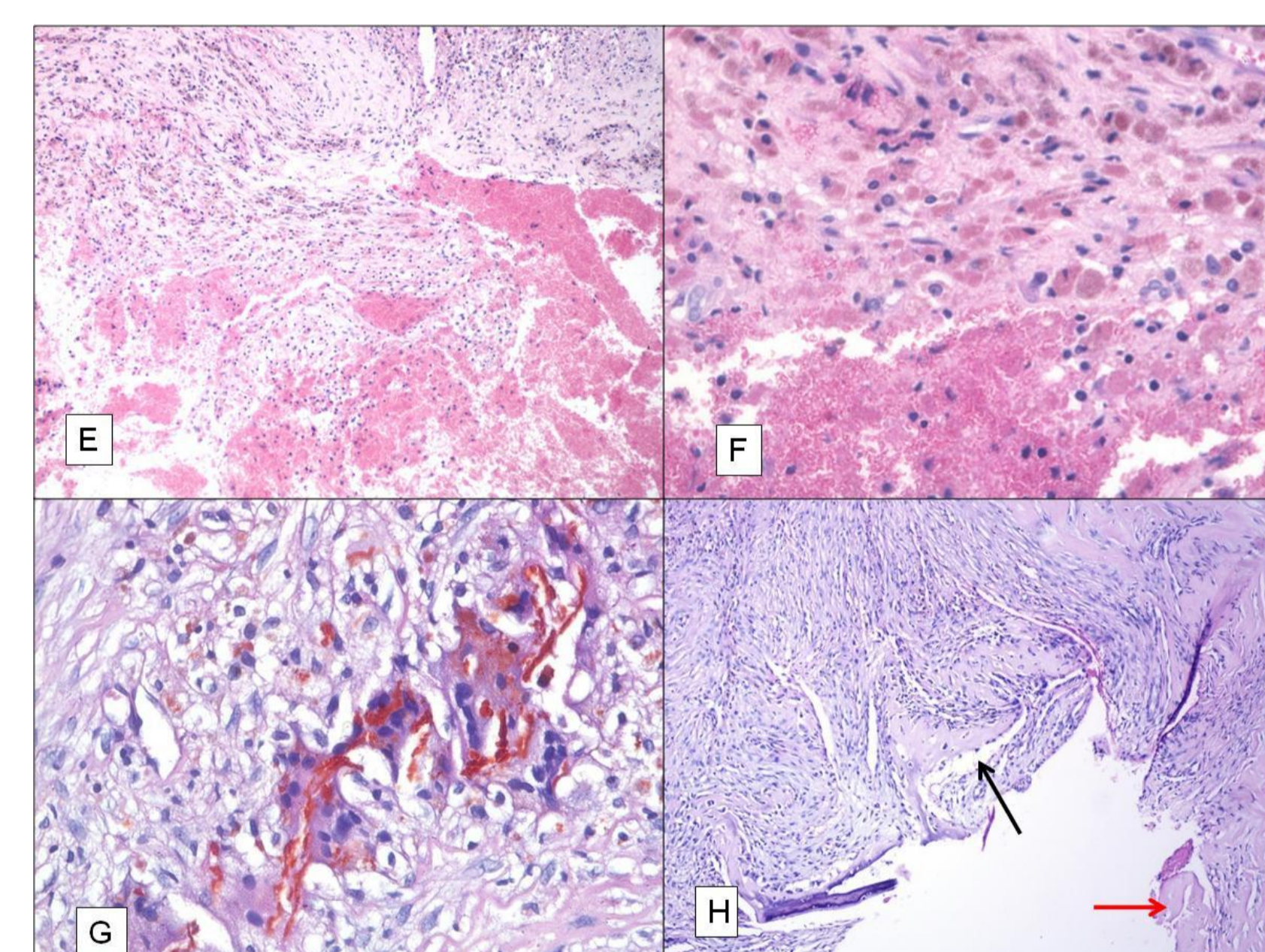
**Fig 1.** Facial image showing the face in the area of both mandibles.



**Fig 2.** Computed tomography scan reveals a lobulated, well-circumscribed heterogenous mass involving both mandibles causing expansion and destruction of the bones. Soft tissues were not compromised.



**Fig 3.** Different views of the cystic areas of the lesion. A and B: low power of the cystic wall, there is some bone remnant in B, surrounded by connective tissue (arrow). D: Blood clotting material next to the wall surface. There are several small capillary vessels next to the surface (arrows)



**Fig 4 .** Other areas showing an irregular cavity, plenty of blood and fibrin inside it, and macrophages with hemosiderin in the thickness of the wall. G: Some multinucleated giant cell conforming foreign body granulomas, related to abundant hemosiderin. H: Reactive osteoblasts at the surface of the remnant bone trabecula (black arrow). Some areas have remarkable hyalinization (red arrow)

## Conclusions

To our knowledge, this is the first reported case of a patient with type 3 VWD and extensive mandibular pseudotumor treated only with VWF/FVIII concentrate (*Humate-P®*) followed by long-term prophylaxis who achieved a complete and sustained bone resolution. Developments in areas of research will refine our understanding of the role played by VWF in vascular and bone biology and pathology.