Clinical report

A 23-year-old female from Northern Macedonia presented with a tumorous swelling of multiple joints and a deformed thumb.

Past history: 2 years – spontaneous wound on the sole of her left foot, healed only after several months of treatment; 7 years – soft tissue calcifications at the right elbow; 10 years – fracture of her left hip requiring surgery with a wound that took 5 years to heal; 16 years – right knee swelling without a known trauma; 17 years – IQ score 60, suspected intellectual disability.

Physical examination:
- alert female patient with a retracted alveolar region, prominent chin, overcrowded teeth with severe caries and thin irregularly lined lips.
- tumor-like, firm swellings (right elbow, knee, ankle); dislocation of distal phalanx of the left thumb), shortened distal phalanges (some fingers); short, subluxated distal phalanges were present
- skeletal survey: severe right elbow and knee anomalies, subluxated joints, destroy articular surfaces and a mixture of sclerosis, massive osteoporosis and bone fragmentation.
- hand films: multiple osteolytic lesions of the end phalanges of some fingers and dislocation of the left thumb

Results and Discussion

Alkaline phosphatase was slightly elevated at 216 U/L (normal range 38–126 U/L). All other studied laboratory tests were normal.

NGS analysis of the patient's DNA: a novel variant in the NTRK1 gene, confirmed by Sanger-sequencing.

To our knowledge, this is the first NTRK1 mutation reported from Macedonia and Southeast Europe.

Bioinformatic pathogenicity prediction tools indicated pathological effects.

ACMG/AMP classification predicted a Class 5 variant. The mother and father of the girl were found to be heterozygous for this novel variant.

A few hundred CNS patients have been reported. The disorder is often diagnosed late, as in this patient.

To date, a total of 108 different NTRK1 mutations have been reported, including missense, nonsense, and splice-site mutations, small insertions or deletions, and gross deletions. Other authors reported further gene alterations.

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Figure 1. Swelling of the right hindfoot, clawing of the toes.

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Conclusion

This novel sequence variant in the NTRK1 gene was not reported previously with CIPA and could possibly represent a founder mutation in Macedonia or Southeast Europe.