Histopathologic evidence that hallux valgus enthesitis does not elicit nail inflammation: is the nail-enthesitis theory still valid?

Sirs,

The hypothesis of an enthesis network of the extensor tendon embracing the nail unit remains a concept widely disseminated in the rheumatological literature (1, 2). The major virtue of this hypothesis is its simplicity with the possibility to suggest an anatomical pathogenic explanation of the association between nail psoriasis and distal interphalangeal (DIP) psoriatic arthritis (1, 2). However, on the basis of histological studies from cadavers (3-5), it has been demonstrated that the proposal of an entheseal tissue of the nail unit corresponds to three different microanatomical structures: the nail dermis and its fibrous root, the subcutaneous proximal nail fold and the periosteum. This new histological representation of the distal phalanx is summarised in Fig.1a.

Research on the histopathology of the enthesitis of the DIP joint is in its infancy due to difficulties in obtaining raw materials.

In a recent study (5), we noted two Caucasian females (56 years and 76 years), who had consented to postmortem scientific research, that had toes hallux valgus deformities without toenail alterations. An additional case was analysed corresponding to a 56-year-old female who presented an extensive interdigital acral melanoma associated with a hallux valgus without nail plate modifications. One hallux cadaver and two lateral toes were analysed. The articular cartilage was relatively well preserved in two specimens and thinned in one. Partial disruption of the insertion of the inferior part of the extensor was observed together with granulation tissue alternating to reparative fibrocartilage (Fig.1c). The dorsal part of the extensor tendon was retained. The discrete inflammatory flow of the enthesis was directed toward the subchondral bone marrow and followed the interface between the proximal inner layer of periosteum and bone with subperiosteal fibrovascular tissue formation (Fig.1c). The matrical hypodermis, the fibrous root of the matrical dermis, and the fascia of the fibrous root were devoid of inflammation. Although in lateral toes, as in the fingers (5), the apex of the matrix is very close to the insertion of the extensor tendon, the two lateral toes did not show inflammatory flow from the enthesis toward the nail unit.

As indicated below, macroscopic examination of the nail plate of these 3 cases does not show nail plate alteration. The growth rate of the nail plate is slow (classically, 1.6 mm/month for toenails), so the potential discontinuous dynamic nature of nail inflammation with alternating areas of

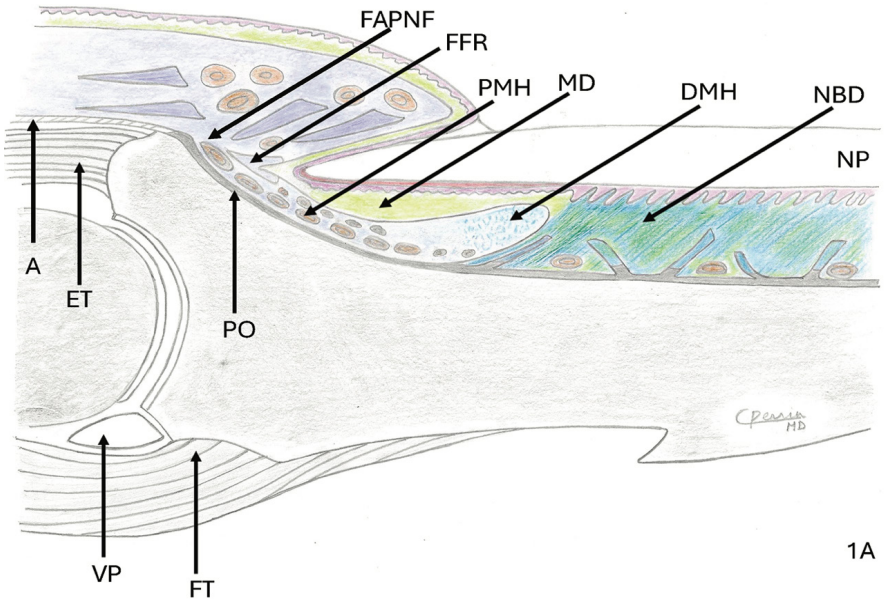

Fig. 1a. The relationship between the distal-interphalangeal (DIP) joint synovio-entheseal complex and nail unit. Normal microanatomy versus hallux valgus enthesitis.
Proposed new textbook image of the normal distal-interphalangeal joint synovio-entheseal complex and nail unit. The nail unit is a skin appendage independent of the DIP joint synovio-entheseal. The DIP enthesis and bone complex are shown in grey to black, and the nail unit as a skin appendage is shown in rainbow. A: aponeurosis of the extensor tendon. ET: extensor tendon; PO: periosteum; VP: volar plate; FT: flexor tendon; FAPNF: fascial and adipose tissue of the proximal nail fold; FFR: fascia of the fibrous nail root; PMH: proximal matrical hypodermis; MD: matrical dermis; DMH: distal matrical hypodermis; NBD: nail bed dermis; NP: nail plate.

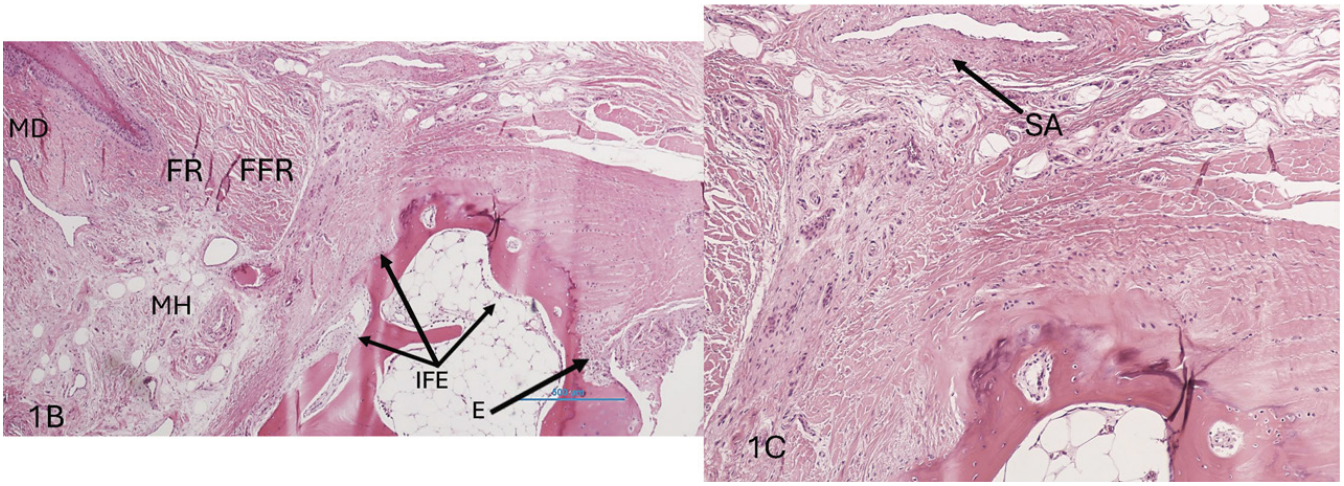

Fig. 1b. Parasagittal longitudinal section of toe 2. Severe enthesitis with destruction of the ventral insertion of the extensor tendon. The discrete inflammatory flow of the enthesis is directed toward the subchondral bone marrow and the inner layer of the periosteum with subperiosteal fibrovascular tissue formation (arrows) (H&Ex40).
E: extensor enthesitis; IFE: inflammatory flow of the enthesitis; MD: matrical dermis; MH: matrical hypodermis; FR: fibrous nail root; FFR: fascia of the fibrous nail root.
Fig. 1c. High magnification of Fig. 1b (H&Ex200). Note the normal and high density of vessels provided by superficial arcade which is the feeder vessel of the proximal matrix and the lack of perivascular inflammation. SA: superficial (proximal) arcade.

inflammation and repair is well assessed when examining the nail plate. The normal nail plate in this study is a clear indicator of the absence of previous matrix inflammation, at least in the preceding 12 months, despite severe enthesitis.

As severe enthesitis occurred without any signs of nail disease, the results of this small case series are in agreement with recent histological studies on nail psoriasis (6-8) which suggest that the radiological findings often observed in DIP PsA at the level of nail psoriasis represent subperiosteal fibrovascular tissue formation, but not a communication between the nail matrix and the DIP joint.

There are reasons to assume that the nail-enthesitis theory is an oversimplified inflammatory model of nail diseases associated with DIP enthesitis. The new histological representation of the distal phalanx summarised in Fig.1a provides additional tools for optimal correlations with radiological imaging.

C. Perrin[1], *MD*
M. Coutts[2], *MD*

[1]*Laboratoire Central d'Anatomie Pathologique, Centre Hospitalier Universitaire de Nice, Hôpital Pasteur, Nice, France;*
[2]*Department of Cellular Pathology, Maidstone Hospital, Kent, UK.*

Please address correspondence to:
Christophe Perrin
Laboratoire Central d'Anatomie Pathologique, Hôpital Pasteur,
30 Avenue Voie Romaine,
06001 Nice, Cedex 1, France.
E-mail: xst.perrin@bbox.fr

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References

1. McGonagle D, Kavanaugh A, McInnes IB *et al*.: Association of the clinical components in the distal interphalangeal joint synovio-entheseal complex and subsequent response to ixekizumab or adalimumab in psoriatic arthritis. *Rheumatology* (Oxford) 2024; 63(11): 315-23. https://doi.org/10.1093/rheumatology/keae060 Erratum in: *Rheumatology* (Oxford) 2024; 63(11): 3198. https://doi.org/10.1093/rheumatology/keae181
2. Tan AL, Benjamin M, Toumi H *et al*.: The relationship between the extensor tendon enthesis and the nail in distal interphalangeal joint disease in psoriatic arthritis--a high-resolution MRI and histological study. *Rheumatology* (Oxford) 2007; 46(2): 253-56. https://doi.org/10.1093/rheumatology/kel214
3. Perrin C: Nail anatomy, nail psoriasis, and nail extensor enthesitis theory: what is the link? *Am J Dermatopathol* 2019; 41(6): 399-409. https://doi.org/10.1097/dad.0000000000001244
4. Perrin C, Coutts M: Concept of onychodermis has no microanatomical basis. *Histopathology* 2024; 84(4): 707-8. https://doi.org/10.1111/his.15089
5. Perrin C: Comparative anatomy of polydactyly and the adult nail unit and its implications in the onychofibroblasts/onychodermis theory. *Am J Dermatopathol* 2024; accepted manuscript.
6. Perrin C: Histological evaluation of the relationships between distal interphalangeal psoriatic arthritis and nail psoriasis: correlations with anatomical studies of the normal nail unit and the main radiological data concerning distal interphalangeal psoriatic arthritis. *Am J Dermatopathol* 2020; 42(12): 911-15. https://doi.org/10.1097/dad.0000000000001786
7. Perrin C: Focal synovial inflammation versus enthesitis theory in distal psoriatic arthritis: a pioneer histopathologic study. *Am J Dermatopathol* 2021; 43(12): 898-902. https://doi.org/ 10.1097/dad.0000000000001947
8. Perrin C: Are there signs of enthesitis in nail psoriasis? An immunohistological study of nail psoriasis with and without psoriatic arthritis. *Am J Dermatopathol* 2023; 45(1): 40-46. https://doi.org/10.1097/dad.0000000000002328