Letters to the Editors

Levels of inflammatory cytokines and metalloproteinases are increased in knee synovial fluid of patients with concomitant erosive hand osteoarthritis

Sirs,

Erosive hand osteoarthritis (HOA) is a subtype of OA targeting interphalangeal joints and characterised by an abrupt onset, marked pain and functional impairment, inflammatory symptoms and signs, and a worse outcome than non-erosive HOA (1, 2). It is still unclear whether erosions represent the local expression of a systemic disease or a consequence of an inflammatory phase of HOA (1, 2).

An association found between erosive HOA and an interleukin (IL)-1β polymorphism (IL1B5810) has supported a potential role for IL-1 in the pathogenesis of severe phenotype of HOA (3). However, low levels of serum IL-1β and a limited involvement of NLRP3 inflammasome has been observed in a small cohort of patients with erosive HOA (4). Furthermore, IL-1-targeted therapies showed contrasting results in treating that disease (5, 6). In fact, while a daily subcutaneous injection of anakinra showed a good response in VAS pain and global handicap in a small case series of patients with erosive HOA (4), a recent phase IIa, placebo-controlled, randomised study of the anti-IL-1α and β lutikizumab failed to show any improvement in pain and function and radiographic progression (6). Similarly, the use of TNF-α inhibitors did not significantly improve the signs and symptoms of erosive HOA in a recent controlled clinical trial (7).

The heterogeneity of OA disease and the large number of molecules involved in the pathological changes in the different joint tissues probably explain the lack of effective treatments and, more importantly, lead to consider OA as a systemic disease (8).

Our study was designed to assess whether patients with erosive HOA have a different phenotype from those with the non-erosive form, investigating the presence of a systemic involvement. For this purpose, we determined the levels of IL-1β and other proinflammatory cytokines and metalloproteinases in synovial fluid (SF) collected from knee joint of patients with erosive and non-erosive HOA.

Consecutive OA patients with knee effusions and history or existing finger pain were enrolled over a two-year period. The patients underwent hand x-rays and were diagnosed as having HOA according to the American College of Rheumatology criteria (9). Those patients with radiographic evidence of at least 1 interphalangeal joint erosion were classified as erosive (10).

Knee SF samples were obtained as part of routine treatment with patient consent under the approval of the institutional review board. After aspiration, SF was analysed by optical light microscopy for total white blood cell (WBC) count determination and the presence of pathogenic crystals. The remaining SF was centrifuged and stored at -80°C for further analysis. Patients with crystals and with other concomitant known joint diseases were excluded from the study. The levels of IL-1β, IL-6, IL-8, MMP-1 and 3 were determined in all SF samples. Statistical analysis was performed by Mann-Whitney non-parametric test and the Spearman test for correlations.

Over the two-year period, we collected 16 SF samples from erosive-HOA and 20 from non erosive HOA knee joint.

As outlined in Table I, the patients with erosive HOA (n=16, 11 females) showed significant higher levels of IL-1β, IL-6, IL-8, MMP-1 and MMP-3 compare to patients without erosions (n=20, 12 females).

As far as correlations between indices were concerned, we found significant correlation between the number of erosions and IL-1β ($p<0.001$; r=0.91), IL-6 ($p<0.05$; r=0.53), MMP-1 ($p<0.05$; r=0.55) and MMP-3 ($p=0.001$; r=0.76) in the erosive HOA patient population.

In this study we found higher levels of cytokines and metalloproteinases in knee OA patients with concomitant radiographic erosive HOA compared to those without erosions. Moreover, inflammatory mediators showed a strong correlation with the number of erosions. These findings confirm the role of inflammation in a particular subset of patients with OA suggesting a systemic interplay among different joints.

Table I. Levels of cytokines and metalloproteinases in knee synovial fluid of the studied patients.

	Erosive HOA	Non-erosive HOA	*p*-value*
no. patients	16	20	
M/F	5/11	8/12	
Age, years	61.69 (7.14)	62.9 (7.03)	NS
Disease duration, years	5.37 (2.98)	4.55 (2.62)	NS
WBC, no./mm^3	746.87 (123.11)	590 (188.90)	<0.05
IL-1ß, pg/ml	16.67 (6.63)	4.52 (2.27)	<0.001
IL-6, pg/ml	551.25 (172.77)	349.6 (126.02)	<0.001
IL-8, pg/ml	154.75 (21.26)	135.3 (8.31)	<0.001
MMP-1, ng/ml	53.81 (17.57)	39.75 (11.18)	<0.01
MMP-3, ng/ml	15.63 (3.46)	10.81 (1.71)	<0.001
no. of erosions	2.56 (1.99)	-	

WBC: white blood cell count; no. of erosions: number of joints with a central erosion; NS: not significant. All values are expressed as mean (DS). *Mann-Whitney test.

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References

1. Punzi L, Frigato M, Frallonardo P, Ramonda R: Inflammatory osteoarthritis of the hand. *Best Pract Res Clin Rheumatol* 2010; 24: 301-12.
2. Punzi L, Favero M, Frallonardo P, Ramonda R: Time to redefine erosive osteoarthritis. *RMD Open* 2015; 1: e000105.
3. Stern AG, De Carvalho MR, Buck GA *et al.*: Association of erosive hand osteoarthritis with a single nucleotide polymorphism on the gene encoding interleukin-1 beta. *Osteoarthritis Cartilage* 2003; 11: 394-402.
4. Fioravanti A, Tenti S, McAllister M *et al.*: Exploring the involvement of NLRP3 and IL-1β in osteoarthritis of the hand: results from a pilot study. *Mediators Inflamm* 2019; 10; 2363460.
5. Bacconnier L, Jorgensen C, Fabre S: Erosive osteoarthritis of the hand: clinical experience with anakinra. *Ann Rheum Dis* 2009; 68: 1078-79.
6. Kloppenburg M, Peterfy C, Haugen IK *et al.*: Phase IIa, placebo-controlled, randomised study of lutikizumab, an anti-interleukin-1α and anti-interleukin-1β dual variable domain immunoglobulin, in patients with erosive hand osteoarthritis. *Ann Rheum Dis* 2019; 78: 413-20.
7. Kloppenburg M, Ramonda R, Bobacz K *et al.*: Etanercept in patients with inflammatory hand osteoarthritis (EHOA): a multicentre, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2018; 77: 1757-64.
8. Robinson WH, Lepus CM, Wang Q *et al.*: Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2016; 12: 580-92.
9. Altman R, Alarcón G, Appelrouth D *et al.*: The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990; 33: 1601-10.
10. Verbruggen G, Wittoek R, van der Cruyssen B *et al.*: Morbid anatomy of 'erosive osteoarthritis' of the interphalangeal finger joints: an optimised scoring system to monitor disease progression in affected joints. *Ann Rheum Dis* 2010; 69: 862-7.