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LETTER

Application of the 2023 ACR/EULAR classification criteria for calcium pyrophosphate deposition disease in a seronegative rheumatoid arthritis cohort

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The 2023 ACR/EULAR Classification Criteria for calcium pyrophosphate deposition (CPPD) disease were recently approved.[1] These criteria used an adjusted domain scoring system including demographic, clinical and radiological characteristics, and synovial fluid crystal analysis. Their development was driven by the necessity to address diagnostic challenges arising from variable clinical presentations and the complexity of analysing synovial fluid seeking for CPP crystals, with their primary purpose being to identify patients eligible for inclusion in research studies.[2] Differential diagnosis of CPPD-disease mostly involves rheumatoid arthritis (RA) for chronic-CPP crystal inflammatory arthritis, gout for acute-CPP crystal arthritis and osteoarthritis (OA) with CPPD (often identified incidentally).[3] Particularly, discerning between chronic-CPP crystal arthritis and seronegative-RA can be challenging due to overlapping joint involvement, seronegativity, potential treatment responses and occasional coexistence.[4–6]

We performed a retrospective cross-sectional analysis within a real-world clinical setting. Our objectives were to evaluate the proportion of patients diagnosed with seronegative-RA who fulfilled the CPPD-disease classification criteria, and to identify demographic and clinical differences among them based on whether they met or not the criteria. The cohort included all patients from an RA clinic who were visited during September to December 2022. Data were collected retrospectively from medical records, including demographic, clinical, serological biomarkers and imaging variables (conventional X-ray and/or ultrasound). The classification criteria were subsequently applied. Statistical analysis included χ^2 tests and t-tests to assess group differences.

We identified 364 RA patients, and excluded those positive for RF and/or anti-citrullinated protein antibodies. The final cohort included 96 patients, 24.4% of the initial sample. Of these, 74.7% were female, with a mean age at symptom onset of 59.3 (±16.4) years and average disease duration of 8.35 years.

Of the 96 patients, 18 (18.9%) met the CPPD-disease criteria. Table 1 summarises their characteristics, based on whether they met or not the criteria.

Patients who met the criteria were older (p=0.048) and exhibited a distinct clinical presentation. Experiencing more than one typical episode of acute arthritis, defined by acute onset/worsening of joint pain with swelling/warmth resolving irrespective of treatment within 14 days, was more common in patients fulfilling the criteria (72.2% vs 33.8%). Within our cohort, none of the patients manifested only one typical episode, likely attributable to the inherent bias in the inclusion criteria, which involved patients with a prior diagnosis of RA known for experiencing recurrent episodes. Joint clinical involvement locations did not significantly differ between the two groups, but majority of the patients who met the criteria exhibited wrist involvement (88.8%), whereas metacarpophalangeal and interphalangeal joint involvement were more common in seronegative-RA without CPPD. In our cohort, none of the patients had positive synovial fluid crystals but we found a highly significant association (p=0.000) between the presence of chondrocalcinosis (CC) and the criteria fulfilment. In our cohort, the identification of imaging evidence of CC demonstrated absolute

Table 1 Characteristics of the sample according to the fulfilment or not of criteria for CPPD disease

	Total (n=95)	Seronegative RA with CPPD disease* (n=18)	Seronegative RA without CPPD disease* (n=77)	P value
Female gender, n (%)	71 (74.7%)	16 (88.8%)	55 (71.4%)	0.142
Age at onset of symptoms (years), p50	63	69.5	61	**0.048**
Disease duration (years), p50	7	7	7	0.952
Time-course and symptoms of inflammatory arthritis†, n (%)				
Persistent inflammatory arthritis	65 (69.5)	13 (72.2)	52 (67.5)	0.010
>1 typical acute arthritis episode	39 (41.1)	13 (72.2)	26 (33.8)	
No persistent or typical inflammatory arthritis	22 (23.2)	1 (5.3)	21 (27.2)	
Sites of inflammatory arthritis†, n (%)				
Wrist	76 (80)	16 (88.8)	60 (77.9)	0.323
MCP	58 (61.1)	10 (55.5)	48 (81.4)	
IP	41 (43.1)	5 (27.7)	36 (46.8)	
Knee	40 (42.1)	5 (27.7)	35 (45.5)	
Feet	29 (30.5)	2 (11.1)	27 (35.1)	
1° MTP	1 (1.0)	0 (0)	1 (1.3)	
Related metabolic diseases, n (%)	0 (0)	0 (0)	0 (0)	N/A
Synovial fluid crystal analysis, n (%)				
Not evaluated	88 (92.6)	18 (100)	70 (90.9)	0.555
MSU crystals+CPP crystals	1 (1.0)	0 (0)	1 (1.3)	
Absence	6 (6.2)	N/A	6 (7.8)	
OA in typical locations, n (%)	16 (16.8)	10 (55.5)	7 (9.1)	0.000
Imaging evidence of CPPD, n (%)	18 (18.9)	18 (100)	0 (0)	0.000
Imaging evidence of erosions, n (%)	29 (30.5)	8 (44.4)	21 (27.3)	0.091
Treatment, n (%)				
Prednisone	21 (21.9)	4 (21.1)	17 (22.1)	0.854
sDMARD	45 (46.9)	10 (52.6)	35 (45.5)	
bDMARD	19 (20)	3 (16.6)	4 (20.8)	
Combination therapy	10 (10.4)	1 (5.3)	9 (11.7)	

Combination therapy: sDMARD+bDMARD.
*According to the new 2023 ACR/EULAR CPPD disease classification criteria.
†Several patients fulfilled >1 item within the B (time-course and symptoms of inflammatory arthritis) and C (sites of typical episodes) domains. However, adhering to instructions for the CPPD classification criteria, only the highest-weighted item was scored.
bDMARD, biological disease-modifying antirheumatic drug; CPP, calcium pyrophosphate; CPPD, calcium pyrophosphate deposition; IP, interphalangeal joints; MCP, metacarpophalangeal joints; MSU, monosodium urate; MTP, metatarsophalangeal joint; OA, osteoarthritis; sDMARD, synthetic disease-modifying antirheumatic drug.

specificity, corroborating the substantial weight assigned to it in the classification criteria. Notably, it is essential to recognise that while radiographic CC supports the diagnosis of CPPD-disease, the absence of such findings does not exclude it, as highlighted in existing literature.[4] Similarly, a significant association (p=0.000) was demonstrated between criteria fulfilment and OA occurring in locations typical of CPPD-disease: bilateral radiocarpal, scaphoid/trapezium/trapezoid without the involvement of trapeziometacarpal, second/third metacarpophalangeal joints. This OA pattern was observed in 55.5% of individuals fulfilling the criteria. Notably, no significant treatment disparities were detected between the subgroups. Among patients positive for CPPD-disease criteria, 74% were treated with disease-modifying antirheumatic drugs.

In summary, our study underscores the importance of imaging within the classification criteria, highlighting its utility in distinguishing between seronegative-RA and CPPD-disease. This distinction is particularly valuable in scenarios where differential diagnosis is challenging, as it may carry important prognostic and therapeutic implications.

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Contributors Study conception and design: HC-M and CD-T. Data collection: HC-M, LS, HSP, HC, CD-T. Analysis and interpretation of results: HC-M, LS, HSP, HC, CD-T. Writing – original draft preparation: HC-M, LS. Writing – review and editing: HC-M, CD-T. Supervision: HC, CD-T.Project administration: HC-M. All authors have read and agreed to the submitted version of the manuscript.

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The data presented in this study are available on request from the corresponding author. The data are not publicly available due to containing clinical and personal information.

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