Is this Prosthetic Joint Infected or Flaring?

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INTRODUCTION:

Diagnosis of a periprosthetic joint infection (PJI) in a patient with inflammatory arthritis (IA) is challenging, as features of IA flares can mimic an infection. We aimed to identify the optimal tests to accurately and efficiently diagnose a PJI in patients with IA.

METHODS:

We included participants in three distinct patient groups: 1) IA patients with a flaring native joint, 2) IA patients with a prosthetic joint undergoing an aseptic revision, and 3) patients with PJI regardless of IA. Demographic characteristics and laboratory values were compared across the three groups using ANOVA or t-tests for continuous variables and chi-square and Fisher's exact tests for categorical variables. Blood and synovial fluid markers were compared across groups to assess the sensitivity and specificity in diagnosing PJI versus IA flares.

RESULTS:

We included participants in three distinct patient groups: 1) IA patients with a flaring native joint, 2) IA patients with a prosthetic joint undergoing an aseptic revision, and 3) patients with PJI regardless of IA. Demographic characteristics and laboratory values were compared across the three groups using ANOVA or t-tests for continuous variables and chi-square and Fisher's exact tests for categorical variables. Blood and synovial fluid markers were compared across groups to assess the sensitivity and specificity in diagnosing PJI versus IA flares.

This study included 52 participants, with 20 IA patients with a flaring native joint, 17 IA patients with a prosthetic joint undergoing an aseptic revision, and 15 patients with gold standard diagnosed PJI undergoing revision. Most were female (60%), and rheumatoid arthritis was the most frequent diagnosis overall (40%) (Table 1). Among the three groups, the confirmed PJI patients were older ($p=0.03$), while no significant statistical differences were observed in the remaining demographic variables.

Synovial fluid and blood markers were significantly different between groups. PJI cases had the highest average C-Reactive Protein (CRP) and there was a significant difference between the groups (PJI: 82 mg/dl, IA flares: 29 mg/dl, aseptic revisions:10 mg/dl, $p<0.05$) (Table 2). Similarly, the percent of synovial fluid polymorphonuclear neutrophils (PMNs) was highest in PJI cases and significantly differed between groups (PJI: 88.9%, IA flares: 54%, aseptic revisions: 17%, $p<0.01$). Among PJI cases, alpha-defensin was positive in 93%. However, positive alpha-defensin was also observed in 20% of flares and 6% of aseptic revisions, with a significant difference ($p<0.01$). There was no significant difference in procalcitonin and IL-6 levels across groups.

Synovial white blood cell (WBC) counts exceeding 3,000 cells/μL, positive alpha-defensin, CRP levels exceeding 3 mg/dl, and PMNs exceeding 80% were highly sensitivity but less specific in diagnosing PJI (Table 3). Synovial WBC counts exceeding 3,000 cells/μL, alpha-defensin positivity, CRP level exceeding 3 mg/dl, and PMNs exceeding 80% were highly sensitive yet less specific for PJI diagnosis. For example, while synovial WBC counts exceeding 3,000 cells/μL and positive alpha-defensin had 100% sensitivity for identifying PJI, their specificity was poor with 50% of IA native joint flares and 79% of aseptic revisions scoring positive for an infection, respectively. The relatively poor specificity of synovial WBC and alpha-defensin indicate that that there is a higher likelihood of these tests incorrectly detecting PJI in cases where it is not present. Positive tests for alpha-defensin or synovial fluid PMNs exceeding 80% increased the likelihood of diagnosing PJI by 5 and 6 times, respectively. However, in cases without PJI, a negative result for PMNs exceeding 80% only marginally increased the likelihood of accurately ruling out diagnosis by 1 time. IL-6, procalcitonin, and D-Dimer demonstrated high sensitivity and specificity, while ESR and CRP exhibited 80% sensitivity but had significantly lower specificity.

DISCUSSION AND CONCLUSION:

Diagnosing PJI in patients with inflammatory arthritis remains challenging. Current efforts are examining whether next-generation sequencing may prove more effective than common clinical tests.

Table 1: Demographic and clinical characteristics of study patients*

	Overall (n=52)	PJI revision (n=15)	IA prosthetic joint revision (n=17)	IA native joint flare (n=20)	p-value**
Age, mean ± SD years	53.4 (18.4)	65.3 (16.8)	57.1 (15.0)	49.0 (17.4)	0.03
Sex, female	31 (59.6%)	10 (66.7%)	11 (64.7%)	10 (50%)	0.63
Medical history					
BMI, mean ± SD	27.7 (5.8)	28.8 (6.2)	30.0 (6.6)	25.8 (4.5)	0.19
Hypertension	20 (38.5%)	4 (26.7%)	10 (58.8%)	6 (30%)	0.14
Heart failure	4 (7.7%)	1 (6.7%)	1 (5.9%)	2 (10%)	1.0
Lung disease	4 (7.7%)	1 (6.7%)	1 (5.9%)	2 (10%)	1.0
Diabetes mellitus Type 1	2 (3.9%)	1 (6.7%)	0 (0%)	1 (5%)	0.74
Chronic Obstructive Pulmonary Disease	2 (3.9%)	1 (6.7%)	0 (0%)	1 (5%)	0.74
Kidney disease	2 (3.9%)	0 (0%)	0 (0%)	2 (10%)	0.32
Inflammatory bowel disease	1 (1.9%)	0 (0%)	0 (0%)	1 (5%)	1.0
Inflammatory arthritis type					
Rheumatoid Arthritis	21 (40.4%)	3 (20%)	8 (47.1%)	10 (50%)	0.15
Psoriatic Arthritis	10 (19.2%)	0 (0%)	5 (29.4%)	5 (25%)	0.05
Ankylosing Spondylitis	4 (7.7%)	0 (0%)	1 (5.9%)	3 (15%)	0.37
Systemic Lupus Erythematosus	4 (7.7%)	1 (6.7%)	3 (17.7%)	0 (0%)	0.13
Gouty arthritis	1 (1.9%)	0 (0%)	0 (0%)	1 (5%)	1.0
Polymyalgia rheumatica	1 (1.9%	0 (0%)	0 (0%)	1 (5%)	1.0
Non-inflammatory arthritis	11 (21.2%)	11 (73.3%)	0 (0%)	0 (0%)	<0.01
Medications					
Nonsteroidal anti-inflammatory drugs	29 (55.8%)	8 (53.3%)	7 (41.2%)	14 (70%)	0.22
Disease modifying antirheumatic drugs	11 (21.2%)	3 (20%)	4 (23.5%)	4 (20%)	1.0
Glucocorticoids	10 (19.6%)	2 (13.3%)	4 (23.5%)	4 (21.1%)	0.83
Biologics	7 (13.5%)	0 (0%)	4 (23.5%)	3 (15%)	0.15
Methotrexate	2 (3.8%)	0 (0%)	2 (11.8%)	0 (0%)	0.18

Except where indicated otherwise values are the number (%) of participants.
***p-value represents the statistical significance of the differences observed in values across the three groups*

Table 2: Synovial fluid and blood markers

	PJI revision (n=15)	IA prosthetic joint revision (n=17)	IA native joint flare (n=20)	p-value*
Hemoglobin g/dL	11.1 (2.1)	12.4 (1.5)	13.3 (1.5)	<0.01
Erythrocyte Sedimentation Rate (ESR) mm/hr	72.4 (44.9)	23.6 (14.7)	41.7 (36.4)	<0.01
C-Reactive Protein (CRP) mg/dL	82.4 (138.4)	9.5 (7.7)	29.3 (39.3)	<0.05
Procalcitonin ng/mL	0.2 (0.3)	0.1 (0)	1.3 (5.5)	>0.10
Interleukin-6 (IL-6) pg/mL	8.1 (12.6)	2.1 (0.3)	10.2 (18.5)	>0.10
Synovial fluid polymorphonuclear neutrophils (PMNs) %	88.9 (8.6)	17.3 (17.6)	54.8 (29.4)	<0.01
Synovial fluid lymphocytes %	8.6 (10.7)	44.8 (7.9)	33.2 (28.5)	<0.01
Synovial fluid culture positive	15 (100%)	0 (0%)	0 (0%)	<0.0001
SARS-CoV-2 Antibody IgG				<0.01
Not performed	2 (13%)	7 (41%)	4 (20%)	
Negative	2 (13%)	9 (53%)	5 (25%)	
Positive	11 (73%)	1 (6%)	11 (55%)	
Alpha-Defensin				<0.01
Not performed	1 (7%)	8 (47%)	6 (30%)	
Negative	0 (0%)	8 (47%)	10 (50%)	
Positive	14 (93%)	1 (6%)	4 (20%)	

**p-value represents the statistical significance of the differences observed in values across the three groups*

Table 3: Sensitivity, specificity, positive likelihood ratio, and negative likelihood ratios of blood and synovial markers for diagnosing prosthetic joint infection*

	Sensitivity (Sn)	Specificity (Sp)	Positive likelihood Ratio	Negative likelihood Ratio
Synovial fluid markers				
Synovial White Blood Cells (>200/uL)	1.000	0.161	1.19	0.00
Synovial White Blood Cells (>3000/uL)	1.000	0.484	1.94	0.00
C-Reactive protein (CRP) (>3.0 mg/L)	0.929	0.565	2.14	0.13
C-Reactive protein (CRP) (>6.9 mg/L)	0.714	0.739	2.74	0.39
Alpha-Defensin positive	1.000	0.792	4.80	0.00
Percentage of polymorphonuclear neutrophils (PMN) (>80.0%)	0.917	0.846	5.96	0.10
Elevated blood markers				
Erythrocyte sedimentation rate (>20 mm/hr)	0.800	0.324	1.18	0.62
Erythrocyte sedimentation rate (>30 mm/hr)	0.800	0.471	1.51	0.42
C-Reactive protein (>10.0 mg/L)	0.800	0.583	1.92	0.34
Interleukin-6 (>2.0 pg/mL)	0.600	0.694	1.96	0.58
D-Dimer (>229 ng/mL)	0.800	0.697	2.64	0.29
Procalcitonin (>.07 ng/mL)	0.133	0.889	1.20	0.98
White Blood Cells (>11.7/nl)	0.067	0.914	0.78	1.02
D-Dimer (>860 ng/mL)	0.333	0.939	5.50	0.71

**The European Bone and Joint Infection Society (EBJIS) 2021 definition served as the gold standard; CRP, serum C-reactive Protein, WBC, synovial white blood cell count; PMN, percentage of polymorphonuclear neutrophils in synovial white blood cell count; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.*