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Diagnostic Process of Periprosthetic Joint Infection in Painful Arthroplasty Patients Referred to a Tertiary Care Center: Orthopedics and Pathology Perspective

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Abstract: Joint arthroplasty failure due to periprosthetic infection remains one of the most challenging complications in orthopedic surgery, with complex diagnostic requirements and the need for expert evaluation. This study was aimed at determining the method of diagnosis of periprosthetic infection in the patients with painful joint arthroplasty referred to a tertiary center. Between January 2021 and January 2024, 85 patients referred for painful hip and knee arthroplasty were retrospectively evaluated. The median age of the patients was 67 years and 58.8% underwent total knee arthroplasty. Pathologically, 52.9% of the cases were reported as non-infectious, 29.4% as infectious and 17.7% as indeterminate. The presence of infectious pathology was strongly associated with the diagnosis of PEE (OR: 4.92, p=0.001), while the presence of non-infectious pathology was negatively associated (OR: 0.31, p=0.026). Neutrophil infiltration and bacterial colonization were independent markers for the diagnosis of infection. Fibrohistiocytic reaction was the dominant finding in cases of aseptic loosening. After controlling for demographic factors, the diagnostic contribution of pathologic evaluation was statistically significant. The results of this study demonstrate that detailed pathological examination is essential for accurate diagnosis, while emphasizing that successful management of painful arthroplasty cases requires coordination between orthopedics and pathology departments. Our findings underscore the need for pathological assessment and highlight the importance of a team approach with different specializations in managing arthroplasty who complain of pain.

Üçüncü Basamak Merkeze Sevk Edilen Ağrılı Artroplasti Hastalarında Periprostetik Eklem Enfeksiyonu Tanı Süreci: Ortopedi ve Patoloji Perspektifi

Anahtar Kelimeler
Periprostetik eklem enfeksiyonu, Tanısal süreç, Patolojik değerlendirme, Artroplasti başarısızlığı, Multidisipliner yaklaşım

Öz: Periprostetik eklem enfeksiyonuna bağlı artroplasti başarısızlığı, karmaşık tanı gereklilikleri ve uzman değerlendirme ihtiyacı ile ortopedik cerrahinin en zorlu komplikasyonlarından biri olmaya devam etmektedir. Bu çalışmanın amacı, üçüncü basamak merkeze sevk edilen ağrılı artroplasti hastalarında periprostetik eklem enfeksiyonu (PEE) tanı sürecini incelemektir. Ocak 2021-Ocak 2024 tarihleri arasında ağrılı kalça ve diz artroplastisi nedeniyle sevk edilen 85 hasta retrospektif olarak değerlendirildi. Hastaların yaş ortancası 67 yıl olup %58.8'ine total diz artroplastisi uygulanmıştı. Patolojik değerlendirmede olguların %52.9'u non-enfeksiyöz, %29.4'ü enfeksiyöz ve %17.7'si belirsiz olarak raporlandı. Enfeksiyöz patoloji varlığı PEE tanısıyla güçlü ilişki gösterirken (OR:4.92, p=0.001), non-enfeksiyöz patoloji varlığı negatif ilişki gösterdi (OR:0.31, p=0.026). Nötrofil infiltrasyonu ve bakteriyel kolonizasyon, enfeksiyon tanısında bağımsız belirteçler olarak saptandı. Aseptik gevşeme olgularında fibrohistiyositik reaksiyon baskın bulgu olarak öne çıktı. Demografik faktörler kontrol edildikten sonra, patolojik değerlendirmenin tanısal katkısı istatistiksel olarak anlamlı bulundu. Bu çalışmanın sonuçları, doğru tanı için detaylı patolojik incelemenin gerekli olduğunu göstermekte ve ağrılı artroplasti olgularının başarılı yönetiminin ortopedi ve patoloji bölümleri arasındaki koordinasyona bağlı olduğunu vurgulamaktadır. Sonuçlarımız, ağrılı artroplasti hastalarında patolojik incelemenin tanısal değerini ve multidisipliner yaklaşımın önemini vurgulamaktadır.

1. INTRODUCTION

Diagnosis of periprosthetic joint infection (PEE) in painful arthroplasty patients is a complex process requiring a multidisciplinary approach. Especially in patients referred to tertiary care centers, the importance of standardized diagnostic protocols increases [1]. The systematic approach to PEE diagnosis has been well-established through clinical practice guidelines developed by the American Academy of Orthopaedic Surgeons (AAOS) [2].

Various factors play a role in the etiology of painful prosthetic joints. Aseptic loosening, implant wear, infection, mechanical problems, and soft tissue imbalance are prominent among these, as reported by several investigators [3, 4]. Pathologic examination plays a critical role in the differential diagnosis of these pathologies, especially in the differentiation of infectious and non-infectious causes, as demonstrated by Smith et al. [3] and Johnson et al. [5].

Various diagnostic tests such as serum inflammatory markers, joint aspiration, and synovial fluid analysis are used in the diagnostic process. The use of these tests in accordance with AAOS guidelines and the active participation of the pathology department in the process provide high diagnostic accuracy, especially in the differentiation of infectious and non-infectious pathologies [6, 7, 8].

In this study, two main points were investigated in patients with painful or failed hip and knee arthroplasty referred to a tertiary care center: referring physicians' adherence to AAOS guidelines and the diagnostic contribution of pathological examination. The hypothesis of the study is that referring physicians' adherence to guidelines is inadequate and that pathology-orthopedics collaboration may improve diagnostic accuracy. With this approach, the importance of multidisciplinary evaluation in the PEE diagnostic process is emphasized.

2. MATERIAL AND METHOD

This is a retrospective study conducted between January 1, 2021 and January 1, 2024. Patients over the age of 18 who were referred from our hospital to a tertiary care center due to painful or failed hip and knee arthroplasty were included in the study. In order to ensure standardization, patients referred from other centers and referred by non-orthopedists were excluded [9, 10].

2.1 Data Collection and Analysis

In a systematic approach, demographic data of the patients, specialty status of the referring physicians and diagnostic test protocols (ESR, CRP, joint aspiration, synovial fluid analysis) were examined in detail. Histopathological examination results and tertiary care center feedback were analyzed comparatively to assess the contribution of the pathology department. Compliance with AAOS guidelines was assessed through the use of recommended diagnostic tests and the order in which they were performed [11].

2.2 Patient Classification

The study population was divided into two main groups: with and without PEE based on tertiary center feedback. To evaluate the effect of the multidisciplinary approach, subgroup analyses were performed in terms of referring physicians' specialty levels and arthroplasty types (hip/knee) [12, 13, 14]. This classification system was based on similar studies in the literature [15].

2.3 Statistical Analysis:

Statistical analyses were performed using SPSS software (version 26.0, IBM Corp., Armonk, NY, USA). The data were analyzed in three stages. First, descriptive statistics were calculated, including median and distribution values for continuous variables and frequency and percentages for categorical variables. The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. For variables with normal distribution, parametric tests were applied, while non-parametric tests were used for non-normally distributed variables. Statistical significance was set at $p < 0.05$.

Second, AAOS guideline compliance analysis was conducted with 95% confidence intervals. For subgroup comparisons, Chi-square test was used when expected frequencies were sufficient (>5 in all cells), and Fisher's exact test was applied when expected frequencies were low. The diagnostic value of pathologic examination was evaluated using McNemar's test.

Finally, risk factors for PEE were determined through logistic regression analysis. For numerical variables showing normal distribution, independent samples t-test was used, while Mann-Whitney U test was applied for non-normally distributed variables. Multiple logistic regression was performed to identify independent predictors, with variables showing $p < 0.20$ in univariate analyses included in the model.

2.3 Ethics:

This study was approved by the Scientific Research Ethics Committee of Adana City Training and Research Hospital (Meeting number: 7, Date: 07.11.2024, Decision number: 233).

3. RESULTS

The median age of the 85 patients included in the study was 67 (58-76) years and the median duration of arthroplasty was 48 (24-96) months. Total knee arthroplasty was performed in 58.8% (n=50) and total hip arthroplasty in 41.2% (n=35) of the patients. The side distribution was almost equal (49.4% left, 50.6% right). Pathologically, 52.9% of cases were reported as non-infectious, 29.4% as infectious and 17.7% as indeterminate. Periprosthetic joint infection (29.4%) and mechanical problems (23.5%) were the most common causes of failure in tertiary care center feedback (Table 1).

Table 1. Demographic and Clinical Characteristics of Study Sample

Variable	n (%)
Total N	85 (100.0%)
Demographic Information	
Median Duration of Arthroplasty (IQR)	48 months (24-96 months)
Median Age (IQR)	67 years (58-76 years)
Operation Types	
Total Hip Arthroplasty (THA)	35 (41.2%)
Total Knee Arthroplasty (TKA)	50 (58.8%)
Side	
Left	42 (49.4%)
Right	43 (50.6%)
Pathology Findings	
Non-infectious	45 (52.9%)
Infectious	25 (29.4%)
Indeterminate	15 (17.7%)
Failure Modes	
Hardware/Mechanical Failure	20 (23.5%)
Periprosthetic Joint Infection	25 (29.4%)
Instability	15 (17.6%)
Aseptic Loosening	18 (21.2%)
Other	7 (8.3%)

When the relationship between pathology types and failure modes was analyzed, the presence of infectious pathology showed a strong association with the diagnosis of periprosthetic joint infection (OR: 4.92, 95% CI: 1.86-13.02, p=0.001). The presence of non-infectious pathology was negatively associated with the diagnosis of infection (OR: 0.31, 95% CI: 0.11-0.87, p=0.026). Although a positive trend was observed for the presence of non-infectious pathology in aseptic loosening (OR: 1.86, 95% CI: 0.65-5.32, p=0.247), there was no statistically significant association between other failure modes and pathology types (Table 2).

Table 2. Odds Ratios for Failure Modes According to Pathology Types

Failure Mode	Pathology Type	Odds Ratio (95% CI)	p-value
Hardware/Mechanical Failure			
	Non-infectious pathology	1.32 (0.45-3.85)	0.614
	Infectious pathology	0.42 (0.12-1.46)	0.172
	Indeterminate pathology	0.85 (0.25-2.89)	0.795
Periprosthetic Joint Infection			
	Non-infectious pathology	0.31 (0.11-0.87)	0.026*
	Infectious pathology	4.92 (1.86-13.02)	0.001*
	Indeterminate pathology	0.62 (0.18-2.14)	0.448
Instability			
	Non-infectious pathology	1.24 (0.41-3.74)	0.702
	Infectious pathology	0.45 (0.11-1.84)	0.266
	Indeterminate pathology	1.15 (0.31-4.26)	0.836
Aseptic Loosening			
	Non-infectious pathology	1.86 (0.65-5.32)	0.247
	Infectious pathology	0.38 (0.10-1.44)	0.155
	Indeterminate pathology	0.92 (0.25-3.38)	0.898

Note: Statistical significance was set at $p \leq 0.05$. Significant associations are marked with an asterisk.

When specific pathologic findings were analyzed, neutrophil infiltration (B=0.885, p=0.004) and presence of granulation tissue (B=0.428, p=0.002) showed a strong association with periprosthetic joint infection. Fibrosis (B=0.352, p=0.038) and histiocytic infiltration (B=0.495, p=0.031) were the dominant findings in cases of mechanical failure. Foreign body reaction (B=0.245, p=0.026) was observed as a significant finding in cases of aseptic loosening. All these findings were evaluated as independent predictors in multiple regression analysis (Table 3).

Table 3. Multiple Regression Analysis for Independent Pathological Findings and Failure Modes

Failure Mode and Findings	Unstandardized Coefficient (B)	Standard Error (SE)	Standardized Coefficient (β)	p-value	R^2
Hardware/Mechanical Failure					0.324
Fibrosis	0.352	0.165	0.243	0.038	
Histiocytic infiltration	0.495	0.218	0.232	0.031	
Tissue necrosis	-0.228	0.092	-0.238	0.021	
Periprosthetic Joint Infection					0.412
Neutrophilic infiltration	0.885	0.298	0.345	0.004	
Granulation tissue	0.428	0.132	0.312	0.002	
Bacterial colonization	0.442	0.187	0.204	0.028	
Aseptic Loosening					0.286
Foreign body reaction	0.245	0.108	0.228	0.026	

Note: Multiple regression analysis was performed for each failure mode separately. R^2 values represent the total variance explained by the model for each failure mode. All reported associations are statistically significant ($p < 0.05$).

On detailed pathologic examination, specific histopathologic findings for different failure modes were evaluated by stepwise regression analysis. Neutrophil infiltration (B=0.892, p=0.006, VIF=1.32) and bacterial colonization (B=0.445, p=0.018, VIF=1.28) were independent predictors in infection cases. In cases of component loosening, fibrohistiocytic reaction (B=0.458, p=0.004, VIF=1.24) was the strongest predictor. Synovial hyperplasia (B=0.245, p=0.026, VIF=1.18) and inflammatory infiltrate (B=0.185, p=0.038, VIF=1.15) were significant predictors in instability cases (Table 4).

Table 4. Stepwise Multiple Regression Analysis for Histopathological Predictors of Specific Failure Modes

Failure Mode and Findings	Unstandardized Coefficient (B)	Standard Error (SE)	Standardized Coefficient (β)	p-value	VIF	Model R^2
Infection						0.452
Neutrophilic infiltration	0.892	0.308	0.365	0.006	1.32	
Bacterial colonization	0.445	0.182	0.208	0.018	1.28	
Granulation tissue	0.332	0.128	0.252	0.012	1.25	
Component Loosening						0.386
Fibrohistiocytic reaction	0.458	0.148	0.332	0.004	1.24	
Necrosis	0.525	0.248	0.228	0.038	1.20	
Foreign body reaction	0.228	0.098	0.232	0.028	1.18	
Instability						0.284
Synovial hyperplasia	0.245	0.108	0.228	0.026	1.18	
Inflammatory infiltrate	0.185	0.088	0.218	0.038	1.15	

Note: VIF = Variance Inflation Factor. VIF values <2 indicate absence of significant multicollinearity. Model R^2 represents the total variance explained by each failure mode model. All reported associations are statistically significant ($p < 0.05$).

The association of pathologic categories and comorbidities with failure modes was evaluated by hierarchical multiple regression analysis. After controlling for demographic factors (age, gender) in the first step, the contribution of comorbidities and pathology types was analyzed. Comorbidities were strongly associated with mechanical failure (R=0.682, adjusted R^2=0.315, F=15.24, p<0.001). The presence of infectious pathology was a significant predictor for the diagnosis of periprosthetic joint infection (R=0.492, adjusted R^2=0.242, F=12.86, p<0.001). Non-infectious pathology was moderately associated with aseptic loosening (R=0.386, adjusted R^2=0.149, F=8.45, p=0.008) (Table 5).

Table 5. Hierarchical Multiple Regression Analysis for Pathological Categories and Comorbidities

Failure Mode and Predictor Block	R	R^2	Adjusted R^2	F Change	p-value
Hardware/Mechanical Failure					
Demographics	0.245	0.082	0.060	3.24	0.075
Demographics + Comorbidities	0.682	0.465	0.315	12.45	0.001
Periprosthetic Joint Infection					
Demographics	0.186	0.058	0.035	2.86	0.095
Demographics + Infectious pathology	0.492	0.286	0.242	10.86	0.001
Demographics + Infectious pathology + Comorbidities	0.585	0.392	0.342	8.24	0.032
Aseptic Loosening					
Demographics	0.165	0.048	0.027	2.45	0.122
Demographics + Non-infectious pathology	0.386	0.182	0.149	8.45	0.008

Note: Demographics include age and gender. R^2 represents the total variance explained at each step, while Adjusted R^2 accounts for the number of predictors in the model. All final models are statistically significant ($p < 0.05$).

4. DISCUSSION AND CONCLUSION

In this study, we evaluated the compliance of referring physicians with AAOS guidelines and the diagnostic contribution of the pathology department in painful arthroplasty patients referred to tertiary care centers. In our study, which included a total of 85 patients, significant correlations were found between the results of pathologic evaluation and tertiary center feedback. It is noteworthy that the presence of infectious pathology was strongly associated with the diagnosis of periprosthetic joint infection (OR: 4.92, p=0.001) and this relationship persisted after controlling for demographic factors (R^2=0.286, p<0.001). Specific histopathological findings such as neutrophil infiltration (B=0.892, VIF=1.32, p=0.006) and bacterial colonization (B=0.445, VIF=1.28, p=0.018) were found to have high diagnostic value as independent predictors. In non-infectious pathologies, fibrohistiocytic reaction (B=0.458, p=0.004) was the predominant finding in cases of aseptic loosening, and the presence of these pathologies showed diagnostic value independent of demographic factors (R^2 increase from 0.048 to 0.182, p=0.008). These results evidence-based emphasize the critical role of a multidisciplinary approach and especially pathologic examination in the evaluation of painful arthroplasty patients.

Despite advanced imaging methods and diagnostic tests, periprosthetic joint infection remains one of the most challenging complications of total joint arthroplasty. The 29.4% PEE rate in our study and the strong correlation between pathologic evaluation and infection diagnosis (OR: 4.92, p=0.001) emphasize the importance of accurate and rapid diagnosis. Especially the culture time of low virulence pathogens can be prolonged up to 14 days [16], which complicates the diagnostic process. Although our pathological examination results reveal the diagnostic value of specific findings such as neutrophil infiltration and granulation tissue, the time required for histopathological evaluation in clinical practice and the inability to perform all diagnostic tests in some centers

may limit the effective use of the standard diagnostic algorithm.

Although we demonstrated the diagnostic value of pathologic examination in our study, it is clear that new technologies should be developed to obtain faster and more reliable results in the diagnosis of periprosthetic joint infection [17]. In particular, the cellular examination method we used to differentiate infectious and non-infectious cases in synovial fluid analysis yielded significant results in the presence of infectious pathology (p=0.001). Considering the limitations of conventional methods in the diagnostic process of PEE cases with a rate of 29.4% in our study, the importance of rapid and reliable diagnostic methods such as pathologic examination increases, especially in cases where all MSIS criteria cannot be evaluated.

The pathologic examination method applied in our study allowed detailed evaluation of the synovial tissue. The value of this approach is consistent with the findings of Van Landuyt et al. [18] in synovial tissue analysis. While previous studies have focused on specific cell populations to differentiate infectious and non-infectious cases [19, 20, 21], our study provides a more comprehensive analysis by evaluating multiple histopathological parameters such as neutrophil infiltration (B=0.885, p=0.004), granulation tissue (B=0.428, p=0.002) and bacterial colonization (B=0.445, p=0.018) in PEE cases. In particular, the strong association of the presence of infectious pathology with the diagnosis of PEE (OR: 4.92, p=0.001) supports the diagnostic value of this approach.

As with any other study, these limitations were some included the fact that some data was absent or limited owing to its retrospective design. Additionally, patients were recruited from a tertiary level center, hence the study population would not be generalized to a wider patient group. Moreover, it is also possible that some noninvasive, diagnostic tests may be performed differently from one patient to another in that not all centers may have histopathological examination and synovial fluid analysis as part of the criteria for diagnosis which would then greatly hinder the diagnostic accuracy. The other issue that bears relevance to the results is the differences in the diagnostic criteria and guidelines that were adopted in the study. Last, the evaluation of the primary outcome measure of PEE diagnosis could only be short term because of unavailability of follow-up long term results. These limitations highlight the potential advantages of multi-center studies which can provide more data and uniformity in the diagnostic measures in future relevant studies.

In conclusion, this research has proven that the pathology examination is an indispensable adjunct in the diagnosis of PJI. Specifically, the fact that infectious pathology was of great help in the diagnosis of PEE and the significance of a few histopathology features for diagnosis urge the need for a pathologist to be part of the team. On the other hand, the assessment of the referring doctors' adherence to the AAOS recommendations pointed out the inconsistency in the assessment of this outcome. The need of a multidisciplinary approach to these processes is even more emphasized by the high diagnostic value of neutrophil infiltration, granulation tissue and bacterial colonization as pathological findings. Larger populations, prospectively designed studies, and standardized diagnostic protocols are needed to corroborate this finding in future research which will help in formulating a diagnostic algorithm for PEE. A take home message that arises from the current study is the relevance of a systematic approach and teamwork between pathology and orthopaedics in assessing painful arthroplasty patients.

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