Clinical and Histopathological Correlation in Cases Undergoing Embolectomy for Acute Extremity Ischemia[*]

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Abstract

Aim: Acute extremity ischemia (AEI) is a disease in which the arterial perfusion of the limb is suddenly reduced, mostly due to a thromboembolic condition. There is a need for an urgent evaluation and intervention, most commonly surgical embolectomy. Surgically removed thrombus materials can provide information about the disease and its process.

Method: Patients who underwent embolectomy for acute extremity ischemia between November 2021 and March 2022 were retrospectively analyzed, and the obtained embolectomy materials were histopathologically evaluated.

Results: We included 32 cases of patients who underwent embolectomy surgery for AEI. The histopathological evaluation of the materials taken from these cases determined that the thrombus age was compatible with the first 48 hours. Malignant epithelial tumor cells were detected in one case. In addition, we assessed and showed that re-intervention was significantly higher in cases with a high fibrin score with chronic peripheral artery disease.

Conclusion: We believe that the histopathological evaluation of the materials removed from patients who underwent embolectomy surgery for acute extremity ischemia can aid in diagnosis, guide treatment, and provide valuable prognostic information.

Keywords: Acute extremity ischemia, embolectomy, fibrin thrombus, histopathology.

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Akut Ekstremite İskemisi Nedeniyle Embolektomi Yapılan Olgularda Klinik ve Histopatolojik Korelasyon

Öz

Amaç: Akut ekstremite iskemisi (AEI), çoğunlukla tromboembolik bir duruma bağlı olarak, ekstremite arteriyel perfüzyonunun aniden azaldığı bir hastalıktır. Çoğunlukla cerrahi embolektomi olmak üzere acil bir değerlendirme ve müdahaleye ihtiyaç vardır. Ameliyatla çıkarılan trombüs materyalleri hastalık ve süreci hakkında bilgi verebilir.

Yöntem: Kasım 2021-Mart 2022 tarihleri arasında akut ekstremite iskemisi nedeniyle embolektomi yapılan olgular retrospektif olarak incelendi ve elde edilen embolektomi materyalleri histopatolojik olarak incelendi.

Bulgular: AEI nedeniyle embolektomi ameliyatı yapılan 32 olgu çalışmaya dahil edildi. Bu olgulardan alınan materyallerin histopatolojik değerlendirmesi sonucunda trombüs yaşının ilk 48 saat ile uyumlu olduğu belirlendi. Bir olguda alınan materyalde malign epitelyal tümör hücreleri saptandı. Ayrıca değerlendirmede kronik periferik arter hastalığı olan yüksek fibrin skorlu olgularda tekrar girişimin anlamlı olarak daha yüksek olduğu görüldü.

Sonuç: Akut ekstremite iskemisi nedeniyle embolektomi ameliyatı geçiren hastalarda çıkarılan materyallerin histopatolojik olarak değerlendirilmesinin tanı ve tedaviye katkı sağlamanın yanı sıra prognostik bilgi sağlayacağı düşünülmektedir..

Anahtar Sözcükler: Akut ekstremite iskemisi, embolektomi, fibrin trombüs, histopatoloji.

Introduction

Acute extremity ischemia (AEI) is a disease that requires urgent evaluation and intervention, in which the arterial perfusion of the extremity is suddenly reduced. Presence of symptoms for less than 2 weeks suggests AEI[1].

Embolism, native artery thrombosis, aneurysm, dissection, and traumatic injury are common causes of AEI. Clinically, viability is evaluated with the Rutherford classification[2].

Risk factors for acute extremity ischemia can be listed as chronic limb ischemia, previous peripheral revascularization, atrial fibrillation (AF), low ankle brachial index (ABI), and comorbidities (such as cancer). In addition to these factors, various demographic (race and country) differences highlight different risk factors[1,3,4].

Aside from the diversity of risk factors and etiology, AEI can be considered especially in 3 groups of patients; 1. Lower extremity thromboembolism, 2. Acute exacerbation of chronic extremity ischemia, 3. Iatrogenic AEI after revascularization. In approximately 70% of cases, symptom duration is less than two weeks, these periods are longer than two weeks in the remaining 30% of the cases[1,3,5].

Comprehensive studies conducted in different countries of the world for a long time indicate that the incidence of disease has been reported to be 1 to 5 per 10,000, 1-year mortality 10-45%, and amputation rates 10-35%[1,4,5].

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The diagnosis is made clinically. It is especially valuable to take a deep anamnesis for the evaluation of chronic background and risk factors. Among imaging methods, computed tomography in particular is the most frequently used modality in terms of specificity, sensitivity, accessibility, therapeutic potential, and extensive anatomical evaluation[1,3,4].

Regarding treatment options, there is often a need for an invasive intervention, together with urgent medical therapy. Although endovascular systems are very advanced and widely used, catheter-mediated surgical embolectomy, defined by Thomas Fogarty in the 1960s, remains a valid treatment among emergency interventions due to the ease of application of the procedure, low costs and lack of need for additional technological equipment[3-6].

The aim of this study is to demonstrate that histopathological examination of thromboembolism material provides valuable guidance in confirming the diagnosis, informing postoperative treatment management, staging ischaemia, and evaluating possibility of recurrence, and short and long-term postoperative morbidity and mortality.

Material and Methods

Patients who underwent embolectomy for acute extremity ischemia in Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital between November 2021 and March 2022 were retrospectively analyzed, and the obtained embolectomy materials were histopathologically evaluated.

Anticoagulant treatment and surgical preparations were started for the patients who were evaluated by a cardiovascular surgeon and diagnosed with AEI by clinical and imaging methods. Detailed information about disease risks and prognosis was given to the patients and their relatives. Then, Fogarty catheter-mediated embolectomy was performed from the appropriate anatomical region.

Antiaggregant and anticoagulant treatment was arranged in the postoperative period. The patients were followed up in the intensive care unit (ICU) and/or ward according to their clinical status. The discharged patients were evaluated in the outpatient clinic controls 1 week later.

Histopathological Evaluation

Thrombus materials obtained during embolectomy were fixed with 10% buffered formalin. All tissues were processed. Sections of 4 μm thickness were prepared, stained with hematoxylin & eosin (H&E, and examined with a light microscope. The evaluated tissues were grouped by scoring in terms of fibrin, polymorphonuclear leukocyte accumulation (PMN leukocytes), and erythrocyte density. For erythrocytes and fibrin, a score of 1 was assigned if they occupied less than 25% of the section surface area, 2 if between 25–75%, and 3 if greater than 75%. PMN leukocytes were scored as 1 if identifiable at ×200 magnification, 2 if identifiable at ×100 magnification, and 3 if identifiable at ×40 magnification.

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Ethical Statement

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Statistical Analysis

Statistical results were obtained using the IBM Statistical Package for the Social Sciences version 21 (SPSS Inc., Chicago, IL, USA) program. Mean±standard deviation was given for continuous variables, percentage and number values were given for categorical variables. The time from the onset of disease symptoms to surgery and the conformity of nonparametric variables to the normal distribution were evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov Smirnov/Saphiro-Wilk). In the case of normal distribution, the groups were compared with the One-way ANOVA test, and then the Tukey test was used for comparison between the groups. In the absence of normal distribution, the groups were compared with the Kruskal-Wallis test. Chi-square and Fisher's exact tests were used to compare categorical variables. Correlation coefficients and statistical significance for the relations between variables that were not normally distributed were calculated by Spearman's test. The p value of <0.05 was considered statistically significant in the results.

Results

Demographic characteristics of 32 patients are listed in Table 1. Femoral (right 13, left 12, bilateral 1) embolectomy was performed in 26 cases. Femoral endarterectomy had to be performed in the same session in three cases. Upper extremity brachial (right 5, left 1) embolectomy was performed in six cases.

Table 1. Case characteristics

	n (%)	**Minimum**	**Maximum**	**Mean ± SD**
Age	year	40	83	63.31 ± 12.83
Sex				
Male	21 (65.6)			
Female	11 (34.4)			
Extremity Claudication				
Yes	8 (25)			
No	24(75)			
Motor deficit				
Yes	3 (9.4)			
No	29 (90.6)			
Sensory deficit				
Yes	13 (40.6)			
No	19 (59.4)			
Rest pain				
Yes	27 (84.4)			
No	5 (15.6)			
Symptom onset	Hours	4	260	41.66 ± 55.89
Rutherford				
Class I	20 (62.5)			
Class IIA	9 (28.1)			
Class IIB	3 (9.4)			

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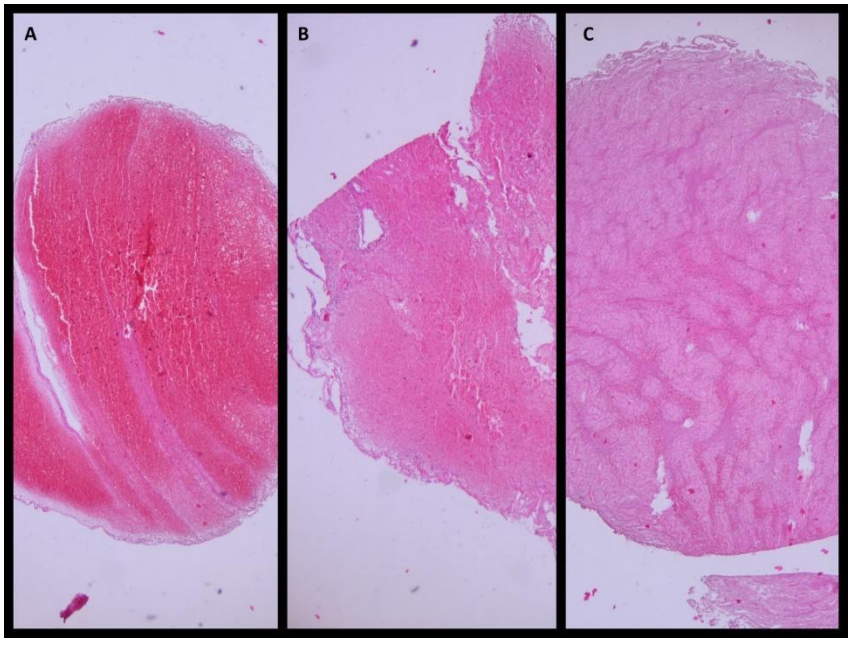
AEI developed in four cases after coronary angiography via femoral artery. In addition, AF/intracardiac thrombus was detected in seven cases and abdominal aortic aneurysm (AAA) in seven cases. 19 patients had symptomatic or asymptomatic chronic peripheral arterial disease.

The histopathological samples showed thrombus ages ranging from 0 to 48 hours. In the examination of embolectomy materials, the fibrin score was 1 in 31.2% of cases. (n=10), 2 in 28.2% (n=9), and 3 in 40.6% (n=13) of cases (Figure 1).

Figure 1. 1A: Fibrin score 1 (<25%) (H&E, x40), 1B: Fibrin score 2(25-75%) (H&E, x40), 1C: Fibrin score 3 (>75%) (H&E, x40)



The erythrocyte score was 1 in 37.4% (n=12), score 2 in 31.3% (n=10), and score 3 in 31.3% (n=10) of cases (Figure 2).

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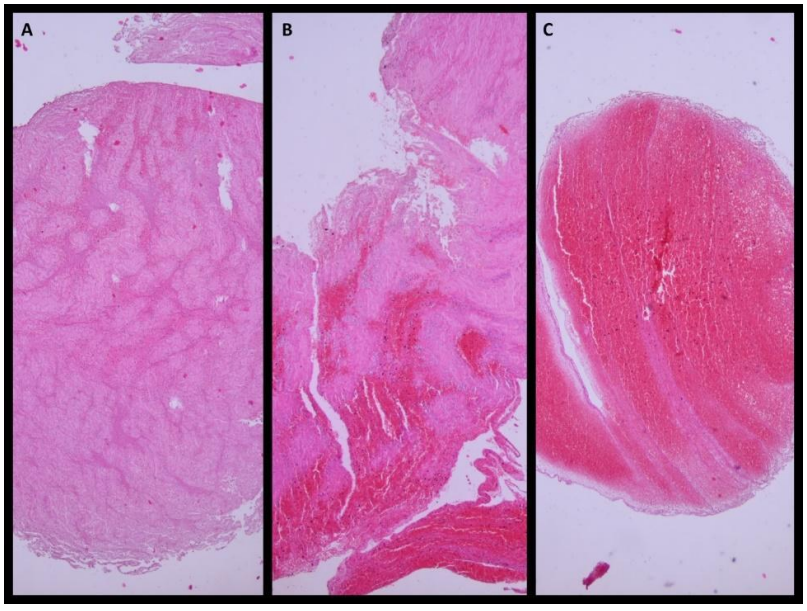
Figure 2. 2A: Erythrocyte score 1 (<%25) (H&E, x40), 2B: Erythrocyte score 2(%25-75) (H&E, x40), 2C: Erythrocyte score 3 (>%75) (H&E, x40)



PMN leukocyte score was found to be 1 in 31.2% (n=10), 2 in 34.4% (n=11), and 3 in 34.4% (n=11) of the cases (Figure 3) (Table 2).

Table 2. Distribution of fibrin, erythrocyte, and PMN scores in embolectomy materials

Fibrin	**n**	**%**
Score 1	10	31.2
Score 2	9	28.2
Score 3	13	40.6
Erythrocyte	**n**	**%**
Score 1	12	37.4
Score 2	10	31.3
Score 3	10	31.3
PMN Leukocyte	**n**	**%**
Score 1	10	31.2
Score 2	11	34.4
Score 3	11	34.4

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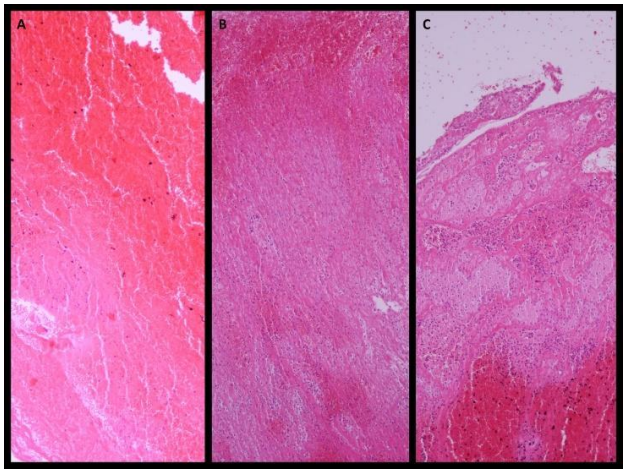
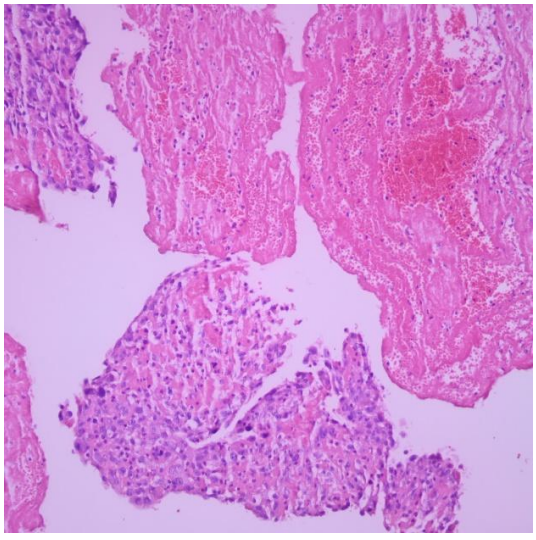
Figure 3. 3A: PMN score 1 (<%25) (H&E, x100), 3B: PMN score 2(%25-75) (H&E, x100), 3C: PMN score 3 (>%75) (H&E, x100)



In one case, tumor cells consistent with a malignant epithelial neoplasm were identified within the fibrin thrombus (Figure 4).

Figure 4. Tumor cells mixed with thrombus (H&E, x200)



No significant correlation was found in the analysis of Rutherford classification, time from symptom onset to surgery, and histopathological scores (Fibrin, eryhtrocyte, PMN leukocyte) (p>0.05)ud

Postoperatively, four of the cases were treated with only acetyl salicylic acid (ASA), five with ASA + clopidogrel, one with clopidogrel + warfarin, and 22 with antiaggregant + LMWH/UFH.

Revision was required due to postoperative bleeding in one case, and wound infection developed in two cases.

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Postoperative reoperation was performed in 10 cases, while amputation was performed in two cases. All-cause mortality was observed in four cases. Regarding mortality, no significant correlation was found between the time from the onset of symptoms to surgery, Rutherford classification, and histopathological evaluation (p>0.05) (Table 3).

Table 3. Correlation analysis of time, Rutherford classification, PMNL score, fibrin score, and reintervention on mortality

	Time	Rutherford classification	PMNL score	Fibrin score	Reintervention
Time					
Correlation Coefficient	***1***	0.329	0.111	0.043	0.017
p – value	-	0.066	0.545	0.817	0.927
Rutherford classification					
Correlation Coefficient	0.329	***1***	0,283	0.032	0.013
p – value	0.066	-	0.117	0.862	0.944
PMNL score					
Correlation Coefficient	0.111	0,283	***1***	0.191	0.054
p – value	0.545	0.117	-	0.294	0.768
Fibrin score					
Correlation Coefficient	0.043	0.032	0.191	***1***	0.249
p - value	0.817	0.862	0.294	-	0.169
Reintervention					
Correlation Coefficient	0.017	0.013	0.054	0.249	***1***
p - value	0.927	0.944	0.768	0.169	-

- Spearman correlation analysis

- PMNL; polymorphonuclear leukocyte

No parameter was found to have a significant relationship with the observed complications. However, a significant correlation was found only with the histopathological fibrin score in the cases treated for AEI with chronic peripheral artery disease (p = 0.042) (Table 4).

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Table 4. Correlation analysis of fibrin score and reintervention

	Reintervention
Fibrin score	
Correlation Coefficient	0.470*
p - value	0.042*

* Spearman correlation analysis, significant correlation

Discussion

AEI is a disease with high mortality and morbidity and early intervention is an important factor influencing the treatment success. Diagnosis is made by the evaluation of the extremity (often the Rutherford classification is used), determining the onset time of the patient's symptoms, and imaging methods. Unfortunately, 30% of AEI cases are diagnosed two weeks or more after the onset of the disease[1,3,5]. Patients presenting to our center with a preliminary diagnosis of AEI were evaluated using the same criteria, their medical treatments were arranged, and the necessary intervention decisions were made.

With the development of technology, the number and success of endovascular interventions have increased. However, in acute cases, it is not always possible to reach experienced centers due to temporal and economic reasons[3,4]. Mostly, catheter-mediated embolectomy surgery has been performed successfully for many years. It is a quick, cost-effective, and relatively easier initiative[1,2,6]. We performed catheter-mediated embolectomy in most of the cases presenting with AEI in our center. We also performed histopathological examination of the thrombus materials obtained through catheter-mediated embolectomy.

Thrombi undergo dynamic changes within days with a mechanism similar to wound repair and pass through the stages of dissemination, embolization, dissolution, organization, and recanalization[7]. During the organization and recanalization, the thrombus stimulates inflammation and fibrosis, vascular flow is restored with recanalization, and the vessel wall thickens. Neutrophils and macrophages are mainly involved in this process[8-11]. In a study conducted with an animal experiment, it was shown that the neutrophil count in the thrombus was at the highest level on the second day[11]. It has been shown that macrophages can be detected in thrombus on the third day at the earliest[12]. Consistent with this, we did not detect macrophages in the embolectomy specimens in our study, which aligns with the fact that all cases were within the first 48 hours and supports findings reported in the literature.

In our study, we scored PMN leukocytes and erythrocytes -among the cellular elements we detected histopathologically in the embolectomy materials- and accompanying fibrin, and compared these scores with the clinical findings of the patients. Thrombus is difficult to date histologically due to differences in approach. Studies have been carried out for many years on the histological reporting of thrombus, and some of these studies are

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autopsy studies[13-18]. While evaluating the thrombus material, the pattern of attachment to the vessel wall, cellular components, hemosiderin deposition, presence and amount of neutrophils, recanalization, integrity and thickness of the vessel affected by the thrombus should also be examined[19]. In a study, it was stated that the thrombus itself, the vessel wall and perivascular tissue, and the central part of the thrombus should be included in the sample for histological analysis[12]. Due to the technique of embolectomy surgery, we made our evaluation by being limited to only the thrombus material, independent of the vessel wall and surrounding tissues. The mean onset of symptoms in the cases included in the study was 41.66 hours. The embolectomy materials we evaluated were also compatible with the first 48 hours. Although there was no relationship with the vessel wall, we had the chance to examine the part closest to the wall by making horizontal sections of the embolectomy material. We evaluated the embolectomy material by sampling and processing the tissue entirely. We think that our systematic examination enabled us to obtain findings consistent with the onset of symptoms.

In the literature, there were studies examining the thrombus materials removed in PTE cases that caused death in autopsy series and endovascularly removed materials in myocardial infarction cases[20,21]. However, we could not find a study in which the histopathological evaluation of the removed thromboembolism material, which is the usual suspect of the disease, was found in patients who underwent embolectomy for AEI. In our study, we showed that the age of the thrombus confirmed the diagnosis of acute embolism because of the examination of the materials obtained from the cases. We also found an incidental presence of malignancy. However, we think that more comprehensive studies and histopathological scoring systems can be developed for prognostic predictions.

Our study has some limitations. Since our study was designed retrospectively, randomization could not be performed. The same treatment could not be applied to every case of AEI, therefore, an evaluation could not be made on the types and rates of interventions. Histopathology samples were not or could not be obtained from each case that underwent embolectomy surgery. In addition, the complexity of the procedure may vary according to the surgeon performing the procedure.

It is important to examine all of the thrombus material removed during the surgery and to perform the microscopic examination by an experienced pathologist. The embolectomy specimens in our study were assessed in this manner; however, the number of cases was relatively small (32), partly due to this meticulous approach.

Conclusion

We believe that the histopathological examination of materials removed from patients undergoing catheter-mediated embolectomy for AEI can provide data supporting the clinical findings. In addition, as highlighted by our study, histopathological evaluation is important in identifying previously undiagnosed malignancies associated with thrombus formation.

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