ORIGINAL ARTICLE

Histopathological evaluation of dental follicles of clinically symptomatic and asymptomatic impacted third molars

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Abstract

Background and Aims: Surgical removal of impacted teeth is a common operation in oral surgery. Thus, pathological potential of impacted third molars is extensively studied. However, many of those studies based on data collected from analysis of radiographs only. The purpose of this retrospective study was to compare the follicles of symptomatic and asymptomatic impacted third molars histopathologically for a number of characteristics.

Materials and Methods: Records of the patients who had been previously operated for impacted third molars were reviewed. Eighty-three patients were selected and divided into two groups, clinically symptomatic and clinically asymptomatic. None of the patients had a radiographic pericoronal radiolucency of wider than 2.5 mm. Histopathological samples of the patients were obtained and re-examined by two pathologists. Two groups were statistically compared for 12 histological parameters.

Results: Eleven of the 12 parameters had statistically significant differences ($P < 0.05$), whereas one parameter (odontogenic remnants) was found not to be significantly different between the groups.

Conclusion: A delay in impacted third molar surgery can lead to further pathological changes in dental follicles and can increase severity of the inflammation. Moreover, dimensions of the pericoronal radiolucency may not provide a correct interpretation of the pathological changes in the region.

Key words: Dental sac, impacted tooth, inflammation, oral surgery, third molar

Date of Acceptance: 02-Nov-2015

Introduction

Surgical removal of symptomatic impacted third molar or prophylactic removal is one of the most frequently performed operations in oral surgery.[1] Nevertheless, debate concerning the indications for removal of impacted third molars has been continuing, which often lead to confusion in the mind of practitioners.[2] Though there are some indications, such as the probability of cystic degeneration or a tumor of the pericoronal follicle, there is no agreement among clinicians about prophylactic removal of them.[3]

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Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/1119-3077.188700

How to cite this article: Esen A, Isik K, Findik S, Suren D. Histopathological evaluation of dental follicles of clinically symptomatic and asymptomatic impacted third molars. Niger J Clin Pract 2016;19:616-21.

Thus, pathological potential of impacted third molars is widely studied. For this purpose, both histopathological and immunohistochemical techniques were used previously.[3,4] However, as far as we know, there are not many studies with control group in the literature associated with the pathological changes occurring in the follicle of impacted third molars. It is usually well known that the absence of pericoronal radiolucency indicates the absence of pathology. Some previous studies suggests that pericoronal radiolucency of <2 mm[5] or <2.5 mm[6] in width is nonpathologic. However, scientific documentation of the validity of this assumption is limited. The purpose of this retrospective study was to histopathologically evaluate the follicles of radiologically normal, but clinically either symptomatic or asymptomatic, impacted third molars.

Materials and Methods

This study was approved by the Ethical Committee for noninvasive clinical trials. Records of 150 patients who underwent the third molar surgery between November 2013 and April 2014 were studied. Tobacco users, alcoholics, and those with systemic diseases that could affect the healing mechanisms were excluded. The remaining patients' records were reviewed, and the ones that had biopsy of the dental follicles (DFs) were noted. Radiolucent area around the impacted tooth was measured on panoramic radiographs, and the patients that have <2.5 mm radiolucency were included in the study. Only 83 patients met the inclusion criteria. Records of clinical signs and symptoms of these patients were re-examined, and they were divided into two groups: Clinically, "symptomatic" (symptomatic group) or "asymptomatic" (control group). A "clinically, symptomatic third molar" was defined as having one or more of the following symptoms such as pain, swelling, trismus, suppuration, and bleeding from the pericoronal tissue. Clinically, asymptomatic teeth had been extracted for prophylactic reasons. All of the patients were followed for 7–10 days. Sutures were removed at the end of this time. Existing biopsy samples of the operated teeth were obtained and re-evaluated, looking for histopathological characteristics listed below. For statistical analyses, Chi-square test with Yates correction was performed, using SPSS version 20. Statistical significance was set at $P < 0.05$.

Histopathological evaluation

The tissues were embedded paraffin blocks, sliced into 5 μm in thickness, and stained with standard hematoxylin-eosin and Masson's trichrome stains. Two oral pathologists, who were not aware of the result of the previous pathology reports and clinical status of the patients, blindly re-assessed each slide for the following histopathological parameters:

- Epithelial atrophy
- Type of epithelial inflammation
- Severity of epithelial inflammation (mild, moderate, and severe)
- Spongious epithelium
- Type of mesenchymal inflammation
- Severity of mesenchymal inflammation (mild, moderate, and severe)
- Erosion/ulcer development
- Odontogenic remnants
- Severity of fibrosis
- Granulation tissue
- Mesenchymal myxoid degeneration (mild, moderate, and severe)
- Squamous metaplasia.

Results

Of the 83 patients, the patients in symptomatic group (n = 48, 58%) aged between 16 and 44 had a mean age of 27.1 ± 6.7 (median 27), whereas patients in control group (n = 35, 42%) aged between 15 and 44 had a mean age of 22.6 ± 6.1 (median 21). There were 33 (69%) women and 15 (31%) were men in the symptomatic group, and 32 (91%) were women and 3 (9%) were men in the control group [Table 1]. Eleven of the 12 histopathological parameters had statistically significant differences while one parameter (odontogenic remnants) was found not to be significantly different between the groups [Table 2]. Epithelial atrophy existed 29% in the symptomatic group and 3% in the control group [Figure 1]. While the type of epithelial inflammation was generally neutrophilic (67%) in the symptomatic group, the control group mostly showed no inflammation (80%). In the symptomatic group, the mild epithelial inflammation rate was 46%, and the severe epithelial inflammation was 42%. However, in the control group, mild and severe epithelial inflammations were 14% and 6%, respectively. Spongious epithelium was seen 69% in the symptomatic group and 11% in the control group [Figures 2 and 3]. Distribution of mesenchymal inflammation types was similar to epithelial inflammation. In the symptomatic group, mixed type was higher (69%) than the control group (9%). Severe mesenchymal inflammation was greater in the symptomatic group than the control group (60% and 11%, respectively) [Figure 4]. Erosion was found to be greater in the symptomatic group (52%) than the control

Table 1: Distribution of symptomatic and asymptomatic groups with impacted third molars according to patient's age and gender

	Symptomatic group	Control group (asymptomatic)
Age±SD	27.1±6.7	22.6±6.1
Males	15	3
Females	33	32

SD=Standard deviation

Table 2: The distribution of the symptomatic and asymptomatic groups by the histologic parameters

Parameter evaluated	Symptomatic (n=48) (%)	Control (n=35) (%)	P
Epithelial atrophy			
Yes	14 (29)	1 (3)	0.005
No	34 (71)	34 (97)	
Type of epithelial inflammation			
No inflammation	6 (13)	28 (80)	<0.001
Neutrophilic	32 (67)	6 (17)	
Mixed	10 (20)	1 (3)	
Severity of epithelial inflammation			
No inflammation	6 (12)	28 (80)	<0.001
Mild	22 (46)	5 (14)	
Severe	20 (42)	2 (6)	
Spongious epithelium			
Yes	33 (69)	4 (11)	<0.001
No	15 (31)	31 (89)	
Type of mesenchymal inflammation			
No inflammation	1 (2)	14 (40)	<0.001
Lymphocyte	14 (29)	18 (51)	
Mixed	33 (69)	3 (9)	
Severity of mesenchymal inflammation			
No inflammation	1 (2)	14 (40)	<0.001
Mild	18 (38)	17 (49)	
Severe	29 (60)	4 (11)	
Ulcer development			
No	15 (32)	34 (97)	<0.001
Erosion	25 (52)	1 (3)	
Ulceration	8 (16)	0 (0)	
Odontogenic remnants			
Yes	12 (25)	7 (20)	0.786
No	36 (75)	28 (80)	
Fibrosis			
Yes	30 (63)	4 (11)	<0.001
No	18 (37)	31 (89)	
Granulation tissue			
Yes	31 (65)	6 (17)	<0.001
No	17 (35)	29 (83)	
Mesenchymal myxoid degeneration			
No degeneration	1 (2)	17 (49)	<0.001
Mild	33 (69)	12 (34)	
Severe	14 (29)	6 (17)	
Squamous metaplasia			
Yes	27 (56)	7 (20)	0.002
No	21 (44)	28 (80)	

Chi-square test with Yates correction was used for statistical analyses

group (3%). Ulcer development was identified 16% in the symptomatic group and 0% in the control group [Figure 5]. Fibrosis was observed 63% in the symptomatic group and 11% in the control group [Figure 6]. Granulation tissue was more common in the symptomatic group (65%) than the control group (17%) [Figure 5]. Mild and severe mesenchymal myxoid degeneration rates were also higher in the symptomatic group (69% and 29%, respectively) than the control group (34% and 17%, respectively). Finally, squamous metaplasia was higher in the symptomatic group (56%) than

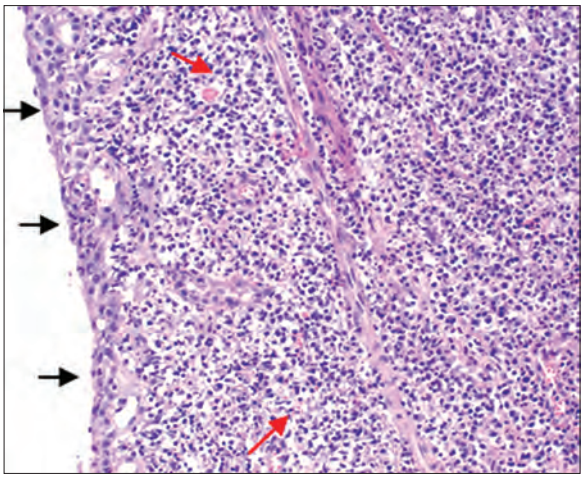

Figure 1: Histological appearance of epithelial atrophy (black arrow: atrophic epithelium, red arrow: mesenchymal inflammation) (H and E, ×100)

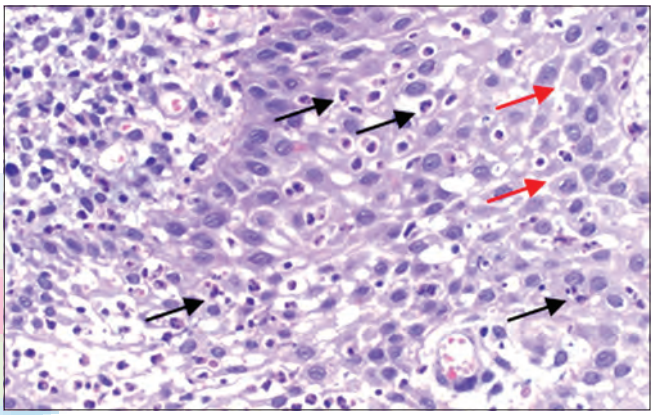

Figure 2: Histological appearance of epithelial inflammation (black arrow: epithelial neutrophiles, red arrow: spongiosis) (H and E, ×200)

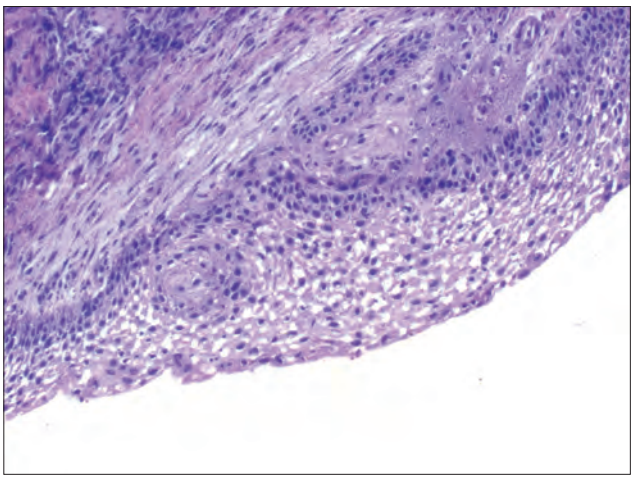

Figure 3: Histological appearance of spongiosis (H and E, ×100)

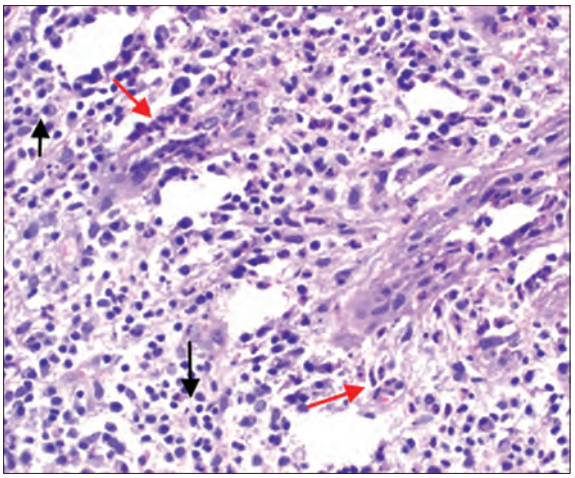

Figure 4: Histological appearance of mesenchymal mixed inflammation (red arrow: neutrophiles, black arrow: mononuclear inflammatory cells-plasmocytes and monocytes) (H and E, ×100)

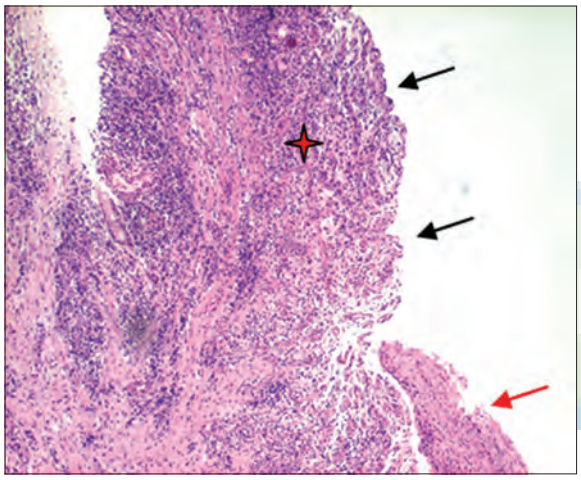

Figure 5: Histological appearance of ulcer development (black arrow: ulcerated area, red arrow: normal epithelium, star: granulation tissue) (H and E, ×40)

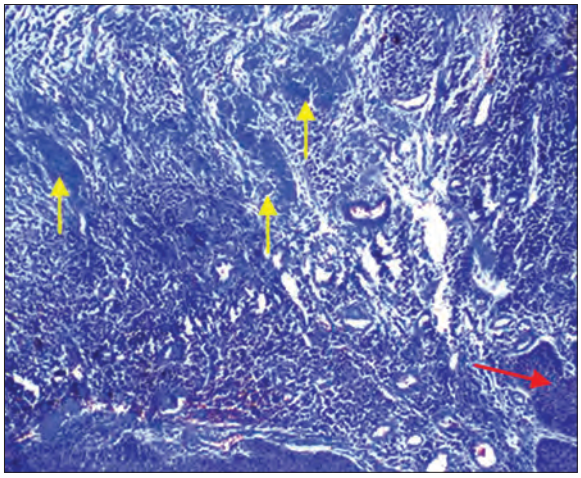

Figure 6: Histological appearance of fibrosis was seen in the subepithelial tissue by Masson's trichrome histochemical staining (red arrow: normal epithelium, yellow arrow: fibrosis areas) (Masson's trichrome × 40)

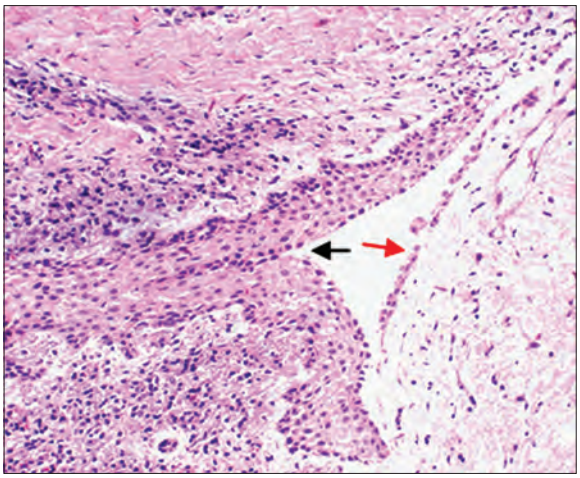

Figure 7: Histological appearance of squamous metaplasia (black arrow: the presence of squamous metaplasia in the infiltration follicle lining, red arrow: intra-cystic normal epithelium) (H and E, ×100)

the control group (20%) [Figure 7]. The rate of the patients who showed cystic changes and were older than 20 years of age was 85% (n = 23 of 27) in the symptomatic group and 71% (n = 5 of 7) in the asymptomatic group.

Discussion

The need for removal of third molars is still controversial. In symptomatic cases, such as pericoronitis, the indication is clear, but scientific basis for removal of asymptomatic third molars is not completely established.[3,7,8] In the assessment of risks and benefits, it is necessary to know the likelihood of pathologic alterations associated with third molars. According to literature, a pericoronal radiolucency of <2–2.5 mm in width is nonpathologic.[5,6,9] Many studies discussing the need for removal of impacted third molars are based on data collected only from analysis of radiographs.[8] In this study, we examined only radiographically normal follicles (<2.5 mm radiolucency) to provide the standardization in both groups. The previous histopathological results of the samples which already existed in the patients' files were reviewed by different pathologists. For the sake of consistency, the samples were re-examined by two pathologists independently, and they decided on the results in Table 2. When cells encounter physiological or pathological stimulus exceeding their physiological limits, they adapt to the new situation depending on the duration or severity of the stimulus. Atrophy is an adaptation mechanism to injury.[10] Distinctive reduction in the number of epithelial cells' layers is considered to be epithelial atrophy, and it was statistically significant in the symptomatic group [Figure 1]. This situation was considered an adaptation of the cells to the inflammatory response in that area. In this study, the type of inflammation was evaluated as acute, chronic, or mixed, which were seen in epithelial and mesenchymal areas.

Acute inflammation is characterized by polymorphonuclear leukocyte infiltration, and chronic inflammation consists of lymphocytes and plasma cells. Acute episode can develop in chronic inflammation with neutrophils included to the scene. Increment of neutrophilic and mixed inflammatory infiltration could be due to acute inflammation which could lead to pain, swelling, and redness [Figures 2 and 4]. Especially if the patient is symptomatic, the overlying oral mucosa may be inflamed, and the inflammation results in epithelial proliferation and spongiosis.[11] Spongiosis is the development of intracellular edema in the epidermis. It may change from increased distance between epithelial cells to bullae or vesicle formation. In our cases, epidermal intercellular distances were increased, and bridges became more prominent, but bullae or vesicles were not seen. Excessive spongiosis could be due to the edema associated with inflammation. [Figures 2 - red arrow and 3]. The result of this study showed that the spongious epithelium was higher in the symptomatic group than the control group. Erosion is an incomplete loss of epidermis, and ulceration is complete loss.[10] In this study, erosion and ulceration were found significantly more in the symptomatic group [Figure 5]. When epithelial damage occurs, fibrosis and granulation tissue develop in subepithelial tissue. These parameters were also higher in the symptomatic group. Fibrosis was evaluated according to the density of staining pattern in the subepithelial tissue by Masson trichrome [Figure 6]. Squamous metaplasia is an adaptation mechanism-like atrophy. It arises as a finding of chronic reversible damage when the cells are constantly affected by nonlethal impulses.[8] Both pathologists diagnosed cystic change as evidenced by the presence of squamous metaplasia in the infiltration follicle lining. The cases that were lined with more than three rows of squamous epithelial cells were considered as positive [Figure 7]. In a previous study,[5] 34% of the samples exhibited squamous metaplasia, and another study[6] also reported 37% squamous metaplasia in follicular specimens. These percentages were lower compared to the 56.3% found in clinically symptomatic cases and higher than the 20% observed in clinically asymptomatic patients. However, in those reports, the only inclusion criterion was to have a pericoronal radiolucency of smaller than 2 mm. It is not clear whether the teeth were clinically symptomatic or not, perhaps those groups were "mixed" with regard to being clinically symptomatic. Yildirim *et al*.[3] reported the rate of cystic changes in asymptomatic impacted third molars as 23%. Furthermore, in another study,[4] in which it was clearly stated that the teeth were clinically asymptomatic, the squamous metaplasia rate was higher (56%) than findings in this study (20%). Their study group seems to be more similar to our clinically asymptomatic group than the previous two studies are. This difference can probably be explained by the difference between the ages of the patients in the study groups. The mean age of our asymptomatic patients was 22.6, whereas it was 28.2 in that study. It has been reported that there is a strong association between age and the incidence of cystic change in follicular tissues as patients advance from age 18 to 21 years.[5,6,12,13] In the aforementioned studies, pathological changes in DFs of asymptomatic impacted teeth had been reported. However, the present study clearly demonstrated that when asymptomatic impacted third molars become symptomatic, not only squamous metaplasia but also severity of inflammation significantly increase. Many of the clinical researches have also evaluated the relationship between pathological changes of pericoronal tissues of the impacted third molars and the patients' age.[3,5,6,13,14] Yildirim *et al*.[3] reported that 89% of squamous metaplasia had been found in patients older than 20 years. Similarly, Baykul *et al*.[14] also reported cystic changes associated with impacted third molars in 56% of the patients older than 20 years of age. In this study, this rate was 85% in symptomatic group and 71% in asymptomatic group in older than 20 years. Based on these findings, we suggest that the risk of cystic changes increases after the second decade. Because of the odontogenic components which have shown a proliferative potential, DF can cause the development of different odontogenic cysts and tumors. Some immunohistochemical studies have shown that inflammation stimulate the proliferation of epithelial cells. Edamatsu *et al*.[15] stated that the inflammation could rearrange the cell turnover of the DF epithelial components. Cabbar *et al*.[4] also reported that the mesenchymal cell inflammation upregulate the cell turnover of odontogenic epithelium and lead to proliferation, and they concluded that inflammation might be effective in squamous changes. In this study, both mesenchymal and epithelial inflammations were higher in the symptomatic group. Therefore, the inflammation more enhances the squamous metaplasia in the symptomatic group than the asymptomatic group. The present histopathological study clearly showed that when asymptomatic impacted third molars become symptomatic, severity of inflammation and squamous metaplasia significantly increase. In addition, spongiosis, erosion/ulcer development, fibrosis, and granulation tissue were found to be greater in the symptomatic group than the asymptomatic group. Thereby, we think that a delay in impacted third molar surgery can lead to further pathological changes in DFs and increase severity of the inflammation. Moreover, radiographic dimension of the pericoronal radiolucency should not always be used as the sole criteria for evaluation of pathological changes around the impacted third molar.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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