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INFLAMMATORY INFILTRATES IN PARATHYROID LESIONS:
CLINICOPATHOLOGICAL ASSOCIATIONS
AND HISTOPATHOLOGICAL CHARACTERISTICS

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Inflammatory infiltrates in parathyroid lesions are uncommon, and their histopathological characteristics and clinicopathological associations remain poorly understood. This study evaluated the frequency, histopathological patterns, and clinicopathological associations of inflammatory infiltrates in parathyroid lesions.

This retrospective study included 121 patients who underwent parathyroidectomy for primary hyperparathyroidism. All available haematoxylin and eosin stained slides prepared from 222 paraffin blocks were independently reviewed by three pathologists. Inflammatory infiltrates were classified using predefined histopathological criteria. Clinicopathological characteristics, biochemical findings, cellular composition, and comorbidities were compared between lesions with and without inflammatory infiltrates. A sensitivity analysis excluding oncocytic adenomas was performed.

Inflammatory infiltrates were identified in 24 of 121 lesions (19.8%) and were predominantly nonspecific. In the overall cohort, inflammatory infiltrates were associated with lower chief-cell and higher oncocytic-cell proportions. However, these associations were not retained after exclusion of oncocytic adenomas, suggesting that they were influenced by lesion subtype. In the restricted analysis, inflammatory infiltrates were associated with a higher clear-cell proportion, although this secondary finding should be interpreted cautiously. No statistically significant associations were observed with clinical characteristics, biochemical parameters, or evaluated comorbidities.

Inflammatory infiltrates were present in approximately one-fifth of surgically resected parathyroid lesions and were predominantly nonspecific and perivascular. Although associations with cellular composition were observed in the overall cohort, these findings were not consistently maintained after accounting for lesion subtype. These exploratory findings require confirmation in larger studies using standardized histopathological criteria.

Key words: inflammation, primary hyperparathyroidism, lymphocytic infiltrate, parathyroid gland, parathyroiditis.

Introduction

Inflammatory disorders of the parathyroid gland are rare; however, focal or nonspecific lymphocytic infiltrates may occasionally be encountered in surgically resected parathyroid lesions. These findings have been described using various terms, including parathyroiditis, lymphocytic parathyroiditis, and lymphocytic infiltration, but standardized diagnostic criteria and classification remain lacking [1]. Consequently, the reported frequency, histopathological features, and clinical relevance of inflammatory infiltrates vary considerably across studies.

Talat *et al.* [1] reviewed the available literature, including autopsy series and case reports, and highlighted the rarity and heterogeneous definitions of inflammatory lesions of the parathyroid gland. Reported frequencies of inflammatory infiltrates differ substantially among studies because of variations in study populations and the absence of uniform morphological criteria. Furthermore, findings from autopsy series are not directly comparable with surgically resected parathyroid lesions because of important methodological differences. In a surgical series of patients with primary hyperparathyroidism, Haglund *et al.* [2] described nodular and diffuse inflammatory infiltrates and investigated a possible viral aetiology; however, no viral transcripts were identified. In addition, several case reports have described associations between parathyroid lesions and inflammation, as well as comorbidities such as autoimmune diseases and malignancies [1, 3–10].

According to the 2022 World Health Organization (WHO) classification, parathyroid lesions include parathyroid adenoma, atypical parathyroid tumour, multiglandular parathyroid disease, and parathyroid carcinoma [11].

The present study aimed to evaluate the frequency and histopathological patterns of inflammatory infiltrates in surgically resected parathyroid lesions and to investigate their associations with clinicopathological characteristics, including autoimmune disease, diabetes mellitus, hypothyroidism, hypertension, and malignancy.

Material and methods

This retrospective single-centre study included consecutive patients who underwent parathyroidectomy at our hospital between 2023 and 2025. A total of 142 patients were initially identified. Seventeen patients with secondary hyperparathyroidism and four patients with tertiary hyperparathyroidism were excluded. Consequently, the final study cohort comprised 121 patients who underwent surgery for primary hyperparathyroidism. The unit of analysis was the individual patient, and each patient was included only once in the statistical analyses. Patients were classified

as having multiglandular parathyroid disease when this diagnosis had been established clinically and was supported by the histopathological findings. Five patients with multiglandular disease underwent concurrent resection of additional tissues because of a preoperative suspicion of parathyroid hyperplasia. However, histopathological examination demonstrated that two specimens represented normal parathyroid tissue, one consisted of fibroadipose tissue, and two consisted of thyroid tissue; these specimens were not included in the study. In addition, two patients had undergone parathyroidectomy before the study period, and those previously resected lesions were not included in the present histopathological re-evaluation; consequently, they were excluded from the analysis.

Clinical data were retrospectively obtained from the hospital information system by endocrinologists (Şafak Akın and Yusuf Kır). Recorded variables included age, gender, preoperative serum parathyroid hormone (PTH), calcium (Ca), phosphorus (P), thyroid-stimulating hormone (TSH), free T4, vitamin D, albumin, creatinine, urinary calcium, and glomerular filtration rate (GFR).

The presence of diabetes mellitus (without differentiation between type 1 and type 2 diabetes), hypothyroidism, hypertension, malignancy, and autoimmune diseases was recorded. Autoimmune diseases included rheumatoid arthritis, Sjögren syndrome, Graves' disease, ankylosing spondylitis, inflammatory bowel disease (Crohn disease and ulcerative colitis), and autoimmune thyroiditis. These comorbidities were analysed as categorical variables based on the documented clinical diagnoses. No independent diagnostic reassessment of these comorbidities was performed for this retrospective study.

All available haematoxylin and eosin (HE)-stained slides from a total of 222 paraffin blocks were re-evaluated. Histopathological evaluation was performed simultaneously by three pathologists (Egemen Akıncioğlu, Hale Kıvrak and Aysu Sadıroğlu) using a multiheaded microscope. The pathologists were blinded to the clinical and laboratory data during the assessment. The final histopathological diagnosis and all evaluated morphological parameters were established by consensus. The proportions of chief, clear, transitional, and oncocytic cells were visually estimated across the entire lesion on HE-stained slides and recorded in 5% increments. Because the relative proportions of the different cell populations are inherently interdependent, cell-type composition was also categorized for descriptive purposes as < 10%, 10–50%, and > 50%.

Because all assessments were performed simultaneously by consensus rather than independently, formal interobserver agreement analyses were not conducted.

Parathyroid lesions were classified according to the 2022 WHO criteria as parathyroid adenoma (PA), multiglandular parathyroid disease/multiple parathy-

roid adenomas, atypical parathyroid tumour (APT), and parathyroid carcinoma [11]. Atypical parathyroid tumour was diagnosed in the presence of worrisome histological features, including adherence to adjacent structures, trabecular or solid growth patterns, cytological atypia, band-like fibrosis, capsular cellular extensions, increased mitotic activity (> 5 mitoses/ 10 mm^2), or atypical mitoses, in the absence of unequivocal invasive criteria. Parathyroid carcinoma was diagnosed based on unequivocal angioinvasion, lymphatic or perineural invasion, direct invasion into adjacent structures, or histologically confirmed metastasis.

The inflammatory infiltrates were evaluated using a study-specific semiquantitative grading system based on the approximate cellularity and architectural organisation of the infiltrate. A lymphocytic aggregate was defined morphologically as a discrete cluster of lymphocytes distinguishable from scattered background lymphocytes. Scattered individual lymphocytes were considered incidental and were not classified as inflammatory infiltrates. Small aggregates composed of approximately 20–49 lymphocytes were classified as mild. Larger aggregates composed of approximately 50 or more lymphocytes, without follicular organisation or a diffuse dense pattern, were classified as moderate. Infiltrates containing one or more well-formed lymphoid follicles or a dense diffuse infiltrate composed of numerous lymphocytes were classified as marked. The distribution of the infiltrate was classified as perivascular, interstitial, follicular, or diffuse, and more than one distribution pattern could be recorded in the same case. The extent of the lymphocytic infiltrate was quantified as lymphoid aggregate density. The entire available lesional tissue was systematically examined using an Olympus BX51 microscope equipped with FN22 oculars and a $4\times$ objective lens. The diameter of a complete $4\times$ microscopic field was 5.5 mm, corresponding to an area of 23.76 mm^2 . Non-overlapping fields containing lesional tissue were counted, and partially occupied fields were estimated as one-quarter, one-half, or three-quarters of a complete field. The total evaluated lesional area was calculated by multiplying the equivalent number of complete $4\times$ fields by 23.76 mm^2 . Lymphoid aggregate density was expressed as the total number of aggregates divided by the evaluated lesional area (lymphoid aggregates/ mm^2). For descriptive purposes, the extent of the infiltrate was categorised using a study-specific semiquantitative classification based on lymphoid aggregate density: mild (< 0.03 aggregates/ mm^2), moderate ($0.03\text{--}0.08$ aggregates/ mm^2), and marked (> 0.08 aggregates/ mm^2).

Inflammatory lesions were classified into three morphological categories: nonspecific lymphocytic infiltrate, follicular lymphocytic parathyroiditis, and destructive/fibrosing lymphocytic inflammation. Follicular lymphocytic parathyroiditis was defined by the presence of one or more well-formed intralesional lymphoid fol-

licles, with or without germinal centres, together with an interstitial lymphocytic infiltrate. Lesions showing prominent fibrosis and/or epithelial destruction without a characteristic follicular pattern were classified descriptively as destructive/fibrosing lymphocytic inflammation (Supplementary Table 1).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a two-sided p -value < 0.05 . Continuous variables were assessed for distributional characteristics using visual inspection of histograms and Q–Q plots together with the Shapiro-Wilk test. Variables demonstrating non-normal distributions were summarised as median and interquartile range (IQR), whereas normally distributed variables were presented as mean $\pm$ standard deviation (SD).

Between-group comparisons for continuous variables were performed according to distributional assumptions. Normally distributed variables were compared using the independent-samples t -test. Welch's t -test was applied when the assumption of homogeneity of variances was violated, as assessed by Levene's test. For non-normally distributed continuous variables, the Mann-Whitney U test was used. Hodges-Lehmann estimates with corresponding 95% CI were calculated to quantify median differences between groups. Effect sizes were reported as rank-biserial correlations (r_{rb}) for Mann-Whitney U tests and Cohen's d for comparisons based on t -tests.

Categorical variables were summarized as frequencies and percentages. Associations between categorical variables were evaluated using Pearson's χ^2 test when the assumptions for asymptotic testing were satisfied. Fisher's exact test or the Fisher-Freeman-Halton exact test was used when expected cell frequencies were insufficient. Effect sizes for categorical analyses were quantified using Cramér's V , and 95% CI were obtained by bootstrap resampling (5,000 samples). For 2×2 contingency tables, odds ratios (ORs) with 95% CI were additionally calculated.

To determine whether the association between inflammatory infiltrate and oncocytic cell proportion was attributable to the inclusion of oncocytic adenomas, a prespecified sensitivity analysis was performed after excluding oncocytic adenomas, atypical parathyroid tumours, and multiglandular parathyroid disease. The relationships between inflammatory infiltrate and cellular composition were subsequently re-evaluated in the remaining conventional parathyroid adenomas using the same statistical approach.

Results

A total of 121 patients were included in the analysis, of whom 97 had no inflammatory infiltrate and

24 had inflammatory infiltrate. The mean age of the cohort was 53.0 ± 11.8 years, and 97 patients (80.2%) were women. Histopathological examination revealed PA in 97 cases (80.2%), atypical parathyroid tumour in 11 cases (9.1%), and multiglandular parathyroid disease in 13 cases (10.7%).

Age and sex distribution were comparable between the groups (Welch's *t*-test, $p = 0.395$). The estimated mean difference in age was 2.86 years (95% CI: -3.91 to 9.63), with a small effect size (Cohen's $d = 0.24$).

Because most biochemical variables were non-normally distributed, they were summarised as median (interquartile range) and compared using the Mann-Whitney *U* test.

Hodges-Lehmann estimates with 95% CI were calculated to quantify the median differences between groups. No statistically significant differences were observed for serum PTH, calcium, 24-hour urinary calcium, serum phosphorus, TSH, free T4, 25-hydroxyvitamin D, creatinine, estimated glomerular filtration rate, or lesion diameter (all $p > 0.05$). The corresponding effect sizes (rank-biserial correlation) were uniformly small, indicating negligible to small between-group differences. Albumin showed a borderline difference between groups (median difference, 0.10 g/dl; Hodges-Lehmann estimate 0.10 g/dl, 95% CI:

0.00 – 0.30 ; Mann-Whitney $U = 859.5$, $p = 0.053$), although this did not reach statistical significance (Table I).

Inflammatory infiltrates were identified in 24 patients (19.8%), including nonspecific lymphocytic infiltrates in 20 patients (Figures 1A, B), follicular lymphocytic parathyroiditis in three patients (Figures 1C, D), and destructive/fibrosing lymphocytic inflammation in one patient (Figure 1E). In cases of follicular lymphocytic parathyroiditis, well-formed lymphoid follicles with prominent germinal centres were observed. The case classified as destructive/fibrosing lymphocytic inflammation showed focal epithelial destruction, fibrosis, and a dense lymphocytic infiltrate. Findings such as hemosiderin-laden macrophages, cholesterol clefts, and fibrosis in three patients were attributed to prior fine-needle aspiration or lesion-related changes and were not classified as lymphocytic infiltrates.

Fibrous bands were observed in 10.7% of patients ($n = 13$), and a trabecular growth pattern was noted in one patient. No angioinvasion, lymphatic or perineural invasion, invasion into adjacent structures, or atypical mitoses were identified.

The frequency of inflammatory infiltrate did not differ significantly according to histopathological diagnosis, including parathyroid adenoma, atypical parathy-

Table I. Clinical and biochemical characteristics according to inflammatory infiltrate status

PARAMETERS	INFLAMMATORY INFILTRATE	N	MISSING	SUMMARY STATISTIC	ESTIMATE (95% CI)	P-VALUE	STATISTICAL TEST	EFFECT SIZE
Age [years], mean $\pm$ SD	Absent	97	0	53.57 ± 10.82	2.86 (-3.91 to 9.63)	0.395	Welch's <i>t</i> -test	$d = 0.24$
	Present	24	0	50.71 ± 15.29				
Gender	Absent	97	0	F/M: 77/20 (79.4%/20.6%)	0.77 (0.24 – 2.51)	0.781	Fisher's exact test	$\phi = 0.040$
	Present	24	0	F/M: 20/4 (83.3%/16.7%)				
PTH [pg/ml]	Absent	97	0	118.0 (87.75–152)	7.0 (-21.0 to 33.8)	0.617	Mann-Whitney <i>U</i> test $U = 1087.0$	$rrb = 0.065$
	Present	24	0	115.65 (73.55–162.50)				
Serum calcium [mg/dl]	Absent	97	0	11.10 (10.80–11.40)	0.0 (-0.3 to 0.3)	0.977	Mann-Whitney <i>U</i> test $U = 1159.5$	$rrb = 0.004$
	Present	24	0	11.15 (10.60–11.58)				
24-hour urinary calcium [mg/24 h]	Absent	77	20	312.50 (220.0–483.36)	-34.7 (-117.53 to 46.6)	0.426	Mann-Whitney <i>U</i> test $U = 716.5$	$rrb = 0.114$
	Present	21	3	420.67 (248.72–492.26)				

Table I. Cont.

PARAMETERS	INFLAMMATORY INFILTRATE	N	MISSING	SUMMARY STATISTIC	ESTIMATE (95% CI)	P-VALUE	STATISTICAL TEST	EFFECT SIZE
Albumin [g/dl]	Absent	96	1	4.40 (4.20–4.60)	0.1 (0–0.3)	0.053	Mann-Whitney U test U = 859.5	rrb = 0.254
	Present	24	0	4.20 (4.10–4.40)			Z: -1.934	
Serum phosphorus [mg/dl]	Absent	95	2	2.50 (2.20–2.90)	-0.1 (-0.3 to 0.3)	0.531	Mann-Whitney U test U = 1045.5	rrb = 0.083
	Present	24	0	2.60 (2.23–3.10)			Z: -0.627	
TSH [μ IU/ml]	Absent	93	4	1.81 (1.21–2.48)	-0.24 (-0.64 to 0.16)	0.232	Mann-Whitney U test U = 939	rrb = 0.159
	Present	24	0	1.90 (1.53–2.61)			Z: -1.195	
Free T4 [ng/dl]	Absent	93	4	1.16 (1.05–1.32)	0.0 (-0.08 to 0.07)	0.938	Mann-Whitney U test U = 1104.5	rrb = 0.010
	Present	24	0	1.20 (1.06–1.30)			Z: -0.078	
25-hydroxy-vitamin D [ng/ml]	Absent	79	18	25.47 (17.00–36.12)	-3.63 (-9.91 to 3.08)	0.236	Mann-Whitney U test U = 654.0	rrb = 0.172
	Present	20	4	29.56 (25.33–38.08)			Z: -1.185	
Creatinine [mg/dl]	Absent	93	4	0.69 (0.61–0.83)	0.04 (-0.02 to 0.11)	0.236	Mann-Whitney U test U = 940.5	rrb = 0.065
	Present	24	0	0.67 (0.57–0.75)			Z: -1.185	
eGFR [ml/min/1.73 m ²]	Absent	92	5	96.50 (79.25–113)	-10.0 (-21.0 to 1.0)	0.063	Mann-Whitney U test U = 831.0	rrb = 0.247
	Present	24	0	106.50 (93.50–124.50)			Z: -1.861	
Lesion diameter [mm]	Absent	97	0	10 (8.00–13.00)	0.0 (-2.0 to 2.0)	0.995	Mann-Whitney U test U = 1163.0	rrb = 0.001
	Present	24	0	11 (9.0–12.32)			Z: -0.007	

eGFR – estimated glomerular filtration rate, F – female, M – male

Data are presented as mean $\pm$ standard deviation (SD) for age and as median (interquartile range [IQR]) for the remaining continuous variables. Welch's *t*-test was used for age, whereas the Mann-Whitney *U* test was used for non-normally distributed continuous variables. Effect sizes are reported as Cohen's *d*, phi coefficient (ϕ), or rank-biserial correlation (rrb), as appropriate. The number of evaluable observations and missing values is presented for each variable. Estimates are reported with 95% confidence intervals (95% CIs).

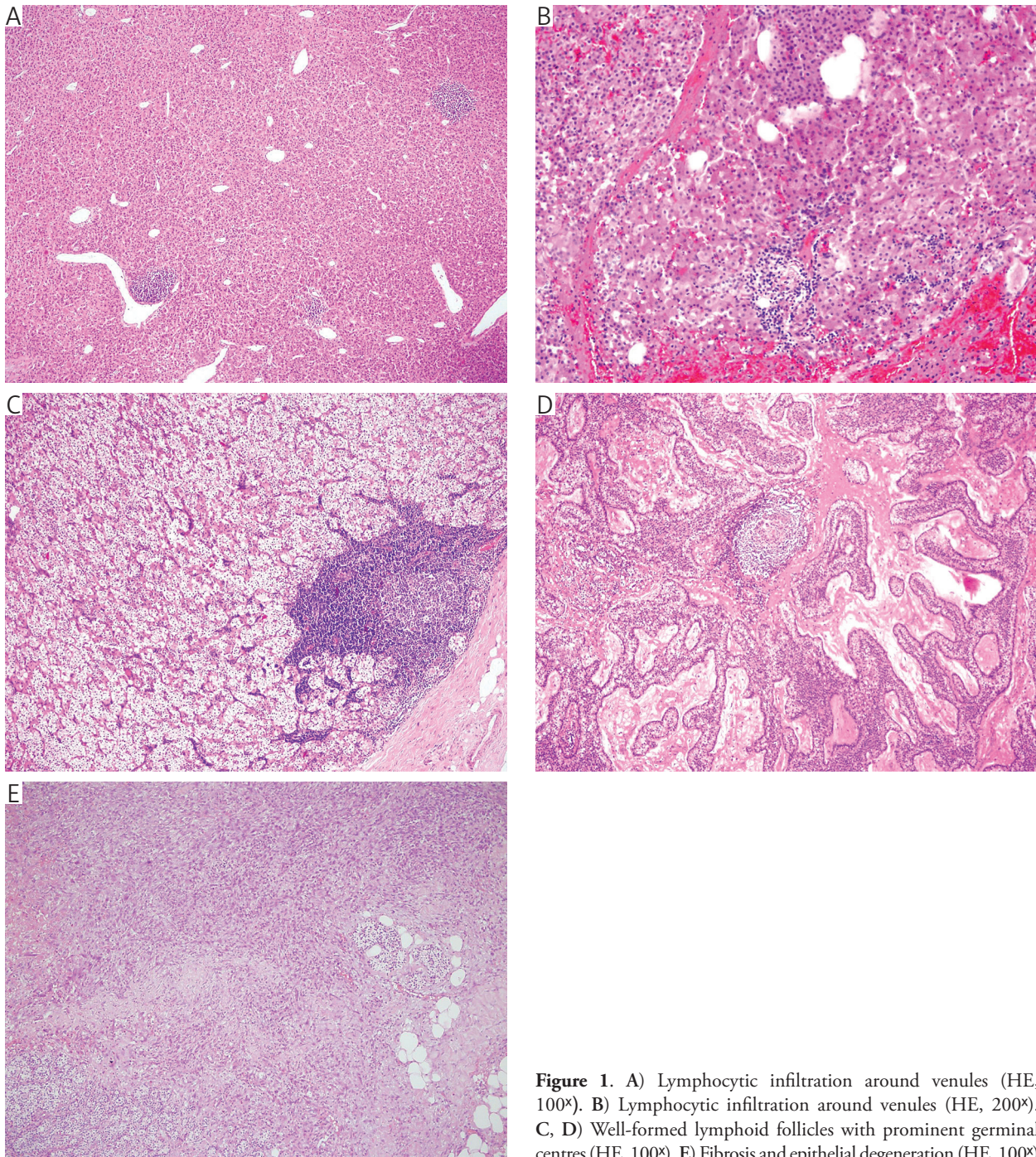


Figure 1. A) Lymphocytic infiltration around venules (HE, 100 $\times$). B) Lymphocytic infiltration around venules (HE, 200 $\times$). C, D) Well-formed lymphoid follicles with prominent germinal centres (HE, 100 $\times$). E) Fibrosis and epithelial degeneration (HE, 100 $\times$)

roid tumour, and multiglandular parathyroid disease (Fisher-Freeman-Halton exact test, $p = 0.187$).

Among the evaluated cellular components, inflammatory infiltrate was significantly associated with the proportion of chief-cells (Pearson's χ^2 test, $p = 0.014$, Cramér's $V = 0.265$, 95% bootstrap CI: 0.108–0.478) and oncocytic cells (Pearson's χ^2 test, $p = 0.016$, Cramér's $V = 0.262$, 95% bootstrap CI: 0.074–0.478). Specifically, inflammatory infiltrate was observed more frequently in lesions containing $> 50\%$ oncocytic cells (50.0%) and in lesions with $< 10\%$ chief-cells (44.4%).

No significant associations were identified between inflammatory infiltrate and the proportions of clear cells ($p = 0.099$) or transitional cells (Fisher-Freeman-Halton exact test, $p = 0.495$) (Table II).

To determine whether the observed association between inflammatory infiltrate and oncocytic cell proportion was driven by the inclusion of oncocytic adenomas, a sensitivity analysis was performed after excluding oncocytic adenomas, atypical parathyroid tumours, and multiglandular parathyroid disease. Among conventional parathyroid adenomas, no significant association was observed between inflam-

Table II. Histopathological characteristics according to inflammatory infiltrate

PARAMETERS	CASES WITH INFLAMMATORY INFILTRATE, n/N (%)	P-VALUE	STATISTICAL TEST	CRAMÉR'S V (95% BOOTSTRAP CI)
Parathyroid adenoma	18/97 (18.6)	0.187	Fisher-Freeman-Halton exact test	0.176 (0.039–0.396)
Atypical parathyroid tumour	1/11 (9.1)			
Multiglandular parathyroid disease	5/13 (38.5)			
Morphological features				
Oncocytic parathyroid adenoma	4/9 (44.4)			
Cystic adenoma	0/3 (0)			
Lipoadenoma	0/2 (0)			
Cellular composition				
Chief cells		0.014	Pearson χ^2	0.265 (0.108–0.478)
< 10	4/9 (44.4)			
10–50	9/28 (32.1)			
> 50	11/84 (13.1)			
Clear cells		0.099	Pearson χ^2	0.195 (0.044–0.413)
< 10	13/71 (18.3)			
10–50	5/35 (14.3)			
> 50	6/15 (40.0)			
Transitional cells		0.495	Fisher-Freeman-Halton exact test	0.105 (0.029–0.324)
< 10	20/100 (20.0)			
10–50	3/19 (15.8)			
> 50	1/2 (50.0)			
Oncocytic cells		0.016	Pearson χ^2	0.262 (0.074–0.478)
< 10	11/76 (14.5)			
10–50	7/33 (21.2)			
> 50	6/12 (50.0)			

Data are presented as n/N (%). Pearson's χ^2 test or Fisher-Freeman-Halton exact test was used as appropriate. Effect sizes are expressed as Cramér's V with bootstrap 95% confidence intervals.

matory infiltrate and the proportions of chief-cells (Fisher-Freeman-Halton exact test, $p = 0.151$; Cramér's $V = 0.196$, 95% bootstrap CI: 0.005–0.476), transitional cells ($p = 0.089$; Cramér's $V = 0.211$, 95% bootstrap CI: 0.115–0.425), or oncocytic cells (Fisher's exact test, $p = 0.360$; Cramér's $V = 0.103$, 95% bootstrap CI: 0.006–0.349). In contrast, a significant association was identified between inflammatory infiltrate and the proportion of clear cells (Fisher-Freeman-Halton exact test, $p = 0.030$; Cramér's $V = 0.287$, 95% bootstrap CI: 0.076–0.539), with inflammatory infiltrate being more frequent in adenomas containing > 50% clear cells (41.7%) than in those with < 10% (10.0%) or 10–50% clear cells (15.4%) (Table III).

The presence of inflammatory infiltrate was not significantly associated with the evaluated comorbidities. Autoimmune disease showed a borderline association with inflammatory infiltrate (odds ratio [OR], 4.91; 95% CI: 1.06–22.67; Fisher's exact test, $p = 0.051$), although statistical significance was not reached. Like-

wise, no significant associations were observed for hypothyroidism (OR, 0.19; 95% CI: 0.02–1.55; Fisher's exact test, $p = 0.167$), hypertension (OR, 1.31; 95% CI: 0.42–4.10; Pearson's χ^2 test, $p = 0.639$), or malignancy (OR, 1.63; 95% CI: 0.28–9.37; Fisher's exact test, $p = 0.627$) (Table IV).

Discussion

Inflammation accompanying parathyroid lesions is often overlooked in routine pathology practice and is infrequently reported. This may be attributable to its rarity, as well as the unclear aetiology, types of inflammation, associated systemic diseases, and clinical significance.

Various classification schemes have been proposed. Ting *et al.* [12] categorized parathyroid inflammation morphologically into nonspecific lymphocytic infiltration, autoimmune lymphocytic parathyroiditis, granulomatous diseases/infections (e.g., cytomegalovirus), and

Table III. Sensitivity analysis of cellular composition according to inflammatory infiltrate in conventional parathyroid adenomas after exclusion of oncocytic adenomas

PARAMETERS	INFLAMMATORY INFILTRATE, <i>n/N</i> (%)	<i>P</i> -VALUE	STATISTICAL TEST	CRAMÉR'S V (95% BOOTSTRAP CI)
Chief cells		0.151	Fisher-Freeman-Halton exact test	0.196 (0.005–0.476)
< 10	1/3 (33.3)			
10–50	5/18 (27.8)			
> 50	8/67 (11.9)			
Clear cells		0.030	Fisher-Freeman-Halton exact test	0.287 (0.076–0.539)
< 10	5/50 (10)			
10–50	4/26 (15.4)			
> 50	5/12 (41.7)			
Transitional cells		0.089	Fisher-Freeman-Halton exact test	0.211 (0.115–0.425)
< 10	13/75 (17.3)			
10–50	0/11 (0)			
> 50	1/2 (50.0)			
Oncocytic cells		0.360	Fisher's exact test	0.103 (0.006–0.349)
< 10	8/60 (13.3)			
10–50	6/28 (21.4)			
> 50	0			

Data are presented as *n* (%). Effect sizes are expressed as Cramér's *V* with bootstrap 95% confidence intervals. Fisher's exact test or Fisher-Freeman-Halton exact test was applied as appropriate.

Table IV. Association between comorbidities and inflammatory infiltrates

COMORBIDITY	<i>N</i>	MISSING	NO INFLAMMATORY INFILTRATE, <i>N</i> (%)	INFLAMMATORY INFILTRATE, <i>N</i> (%)	TOTAL	OR (95% CI)	<i>P</i> -VALUE	STATISTICAL TEST
Autoimmune disease	73	48	4 (50.0)	4 (50.0)	8	4.909 (1.063–22.672)	0.051	Fisher's exact test
Hypothyroidism	73	48	16 (94.1)	1 (5.9)	17	0.188 (0.023–1.545)	0.167	Fisher's exact test
Hypertension	73	48	27 (77.1)	8 (22.9)	35	1.312 (0.420–4.095)	0.639	Pearson χ^2 test
Malignancy	73	48	5 (71.4)	2 (28.6)	7	1.631 (0.284–9.370)	0.627	Fisher's exact test
Diabetes mellitus	74	47	24 (82.8)	5 (17.2)	29	0.729 (0.221–2.403)	0.603	Pearson χ^2 test

Data are presented as *n* (%). Odds ratios with 95% confidence intervals are reported. Pearson's χ^2 test or Fisher's exact test was applied as appropriate.

invasive sclerosing parathyroiditis. Another study classified inflammation as diffuse or nodular infiltration [2]. In the present study, inflammatory infiltrates were classified morphologically into three categories: non-specific lymphocytic infiltrate, follicular lymphocytic parathyroiditis, and destructive/fibrosing lymphocytic inflammation. This study-specific classification was based on predefined histopathological criteria to distinguish nonspecific inflammatory infiltrates from follicular and destructive inflammatory patterns.

Recent studies suggest that chronic inflammation may contribute to the pathogenesis of PA through my-

eloid cell infiltration and the formation of a proinflammatory microenvironment involving fibroblasts, endothelial cells, and macrophages [13]. However, in our study, lymphocytic infiltrate was not more frequent in PA compared with other lesion types; in fact, the incidence of inflammation was slightly higher in multiglandular parathyroid disease.

Lymphocytic infiltrate was present in 19.8% of cases in our cohort. Lymphocytic parathyroiditis accounted for 12% of cases, and 4% of destructive/fibrosing lymphocytic inflammation, while lymphocytic infiltrate constituted 83.3%. The observed frequency was broadly

comparable with some previous reports, although differences in study populations and histological definitions limit direct comparison [1, 2].

Kovacs *et al.* [10] reported fibrosis and loss of parathyroid cells in patients treated for breast carcinoma. In contrast, Haglund *et al.* [2] did not observe parathyroid degeneration or fibrosis and suggested that these findings were independent of inflammation. In our series, three patients with follicular lymphocytic parathyroiditis had comorbidities, including diabetes mellitus/hypothyroidism, rheumatoid arthritis, and osteoporosis. The patient with destructive/fibrosing lymphocytic inflammation had a history of diabetes mellitus, hypertension, lymphoma, and benign prostatic hyperplasia. Although a similar observation has been reported by Kovacs *et al.* [10], the aetiology of this inflammatory pattern remains uncertain. A possible relationship with previous lymphoma therapy cannot be excluded; however, the retrospective nature of the present study does not permit any causal inference.

Granulomatous inflammation is extremely rare; to our knowledge, only nine case reports and one series of 14 cases have been described, with etiologies including tuberculosis, sarcoidosis, and fungal infections [1, 5–7]. Interestingly, in two reported cases, the underlying cause could not be identified, and no evidence of disease was observed during postoperative follow-up [8, 9]. The absence of granulomatous inflammation in our study is probably attributable to its rarity.

Previous studies have reported no association between parathyroid inflammation and age, gender, or serum calcium and phosphate levels [2]. Similarly, we found no association between parathyroid inflammation and demographic characteristics or preoperative biochemical parameters. Talat *et al.* [1] suggested that nonspecific inflammation may result from an exaggerated immune response associated with septicæmia or septic shock, capillary damage leading to oedema, intravascular protein loss, and lymphocytic extravasation. In addition, serum albumin is recognized as a marker of inflammation and functions as a negative acute-phase reactant [14]. Consistent with the literature, most of our cases (83.3%, $n = 20/24$) exhibited diffuse lymphocytic infiltration around venules, with nonspecific lymphoid infiltrates scattered among parathyroid cells. In our study, serum albumin levels were within the reference range in both groups, and no statistically significant difference was observed. Therefore, no biological interpretation can be drawn from this finding.

Chief-cells predominate in parathyroid lesions, whereas clear, oncocytic, and transitional cells are less common [15]. In our study, inflammation was associated with an increased proportion of oncocytic cells and a decreased proportion of chief-cells, consistent with the findings of Haglund *et al.* [2]. Oncocytic parathyroid adenomas (OPA) accounted for 9.2% of PAs in our

series, and inflammation was present in 44.4% of OPA cases – a rate higher than the overall frequency. However, these associations were not retained in the sensitivity analysis performed after exclusion of oncocytic adenomas, suggesting that the findings in the overall cohort may have been influenced by the inclusion of this histological subtype. In the restricted analysis of conventional parathyroid adenomas, no significant association remained for chief-cell or oncocytic-cell proportions, whereas inflammatory infiltrates were more frequent in lesions with a higher clear-cell proportion. This finding should be interpreted cautiously because it emerged from a secondary sensitivity analysis and requires confirmation in larger cohorts. The cross-sectional design also precludes determination of whether inflammatory infiltrates contribute to changes in cellular composition, whether particular cellular phenotypes preferentially attract inflammatory cells, or whether both reflect a shared underlying biological process.

Primary hyperparathyroidism has been associated with immunosuppression and an increased risk of malignancy [16]. In our cohort, the overall malignancy rate was 5.8%, including two patients with inflammatory infiltrates (papillary thyroid carcinoma and lymphoma) and five without inflammatory infiltrates (polycythæmia vera, lymphoma, bladder carcinoma, ovarian carcinoma, and malignant melanoma). Given the small number and heterogeneous spectrum of malignancies, no conclusions regarding specific associations between inflammatory infiltrates and particular malignancy types can be drawn. Although autoimmune disease showed a trend toward a higher frequency among patients with inflammatory infiltrates, this finding did not reach statistical significance and should be interpreted cautiously because of the limited number of affected patients.

No statistically significant associations were identified between inflammatory infiltrates and the evaluated comorbidities, including hypothyroidism, diabetes mellitus, and hypertension. However, these findings should be interpreted with caution because the number of patients with individual comorbidities was small, limiting the statistical power to detect modest associations. Therefore, the absence of statistically significant associations should not be interpreted as evidence of the absence of a biological relationship, and larger studies are needed to further clarify potential associations.

The strengths of this study include the systematic re-evaluation of lymphocytic infiltrates by three pathologists using predefined morphological criteria and the integrated evaluation of clinical, biochemical, and histopathological findings in a well-characterised cohort of patients with primary hyperparathyroidism.

This study has several limitations. First, its retrospective, single-centre design may limit the general-

isability of the findings. Second, the number of cases fulfilling the morphological criteria for follicular lymphocytic parathyroiditis was small, limiting subgroup comparisons. Although the extent of inflammation was quantified using aggregate density expressed as aggregates per square millimetre, the applied cutoff values were developed specifically for the present study and have not been externally validated. In addition, the proportions of chief, clear, transitional, and oncocytic cells were visually estimated across the entire lesion, and no formal interobserver agreement analysis was performed; therefore, some degree of observer-dependent variability cannot be excluded. Multiple exploratory statistical comparisons increase the possibility of type I error, and no multivariable adjustment was performed for potential confounding factors. Furthermore, comorbidity data were obtained retrospectively from electronic medical records and may have been incomplete or heterogeneous. Finally, the cross-sectional nature of the study does not allow determination of temporal relationships or causal mechanisms underlying the observed associations.

Conclusions

Inflammatory infiltrates were identified in approximately one-fifth of surgically resected parathyroid lesions and were predominantly nonspecific and perivascular. In the overall cohort, inflammatory infiltrates were associated with lower chief-cell and higher oncocytic-cell proportions; however, these associations were not retained in the sensitivity analysis restricted to conventional parathyroid adenomas after exclusion of oncocytic adenomas. A higher clear-cell proportion was associated with inflammatory infiltrates in the sensitivity analysis, but this secondary finding should be interpreted cautiously. No statistically significant clinical or biochemical associations were demonstrated. These exploratory findings require confirmation in larger studies using standardized histological criteria, reproducibility assessment, and analyses that adequately account for parathyroid lesion subtype.

Disclosures

1. Institutional review board statement: This study was approved by the Ethics Committee of the University of Health Sciences, Gülhane Training and Research Hospital Non-Interventional Scientific Research Ethics Committee (approval decision no: 2025/15, dated: 16.01.2025).
2. Assistance with the article: This study was presented as an oral presentation at the 34th National Congress of Pathology, held on November 12–16, 2025, in Belek, Antalya, Turkey.
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4. Conflicts of interest: None.

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