



## Follicular cystitis: a review of the literature with several cases

Caner Ediz<sup>1</sup>, Ayse Nur Ihvan<sup>2</sup>, Hakan Remzi Dincer<sup>1</sup>

<sup>1</sup>Üsküdar State Hospital, Department of Urology, İstanbul, Turkey

<sup>2</sup>Üsküdar State Hospital, Department of Pathology, İstanbul, Turkey

### Abstract

Follicular cystitis (FC) is a benign pathology of bladder surface and has a proliferative character. It is an entity that belongs to the group of chronic cystopathies. FC were identified by Cruveillier for the first time in the year 1856. Bacterial infections and inflammatory process are believed to be responsible for the etiology. Patients present with non-specific lower urinary tract symptoms such as dysuria, hematuria and pollakiuria. But recurrent urinary tract infection or resistant microscopic or macroscopic hematuria attacks can be stimulating for the diagnosis of FC. Usually, radiological imaging methods don't help to diagnosis. The real diagnosis of FC consists of cystoscopy planning followed by histopathological examination. In the cystoscopy, mostly the presence of nodules in trigone localization can be detected. The presence of large number of plasmatic cells and lymphocytes in lymphoid follicles in trigonal area mucosa and submucosa of bladder are typical characteristics of FC. So, pathological examination is necessary for the final diagnosis of this entity. Conservative management is the best and most applied method in treatment. Notwithstanding the preferred approaches in conservative treatment options, radiotherapy and cystectomy can be applied in refractory cases. In our study, we evaluate current approaches with several cases with follicular cystitis and alternative treatment options with accompanying guidelines to treat this entity.

**Keywords:** Follicular Cystitis; Diagnosis; Treatment; Update.

Follicular cystitis is a rare type of cystitis that is more common in women. Although its etiology has not been fully clarified, inflammatory processes and bacterial infections have been determined to be influential in the etiopathogenesis (1). In a great portion of follicular cystitis cases, there are no disease-specific symptoms. Dysuria, pollakiuria, hematuria, and recurrent urinary tract infections are the most common complaints. The contribution of laboratory findings and imaging methods is extremely limited in the diagnosis. Flat or papillary lesions superficial or nodular in character and erythematous and velvety in appearance are observed macroscopically inside the bladder in the cystoscopy. Because some cases can be confused with bladder cancer, they are macroscopically identified as pseudoneoplasms. Germinal centered lymphoid follicles were identified by Cruveillier for the first time in the year 1856. It is characterized by a germinal centered lymphocytic infiltration localized in the bladder lamina propria (3, 4). Follicular cystitis treatment is similar to other types of chronic cystitis. It is aimed to suppress the inflammation as a result of taking of antibiotics and anti-

inflammatory medication. Follicular cystitis, from the day that it was identified, has been a pathology that is always open to speculative opinion in terms of its etiology, treatment and prognosis. Our aim in this review is to talk about updates in diagnosis and treatment, with reference to follicular cystitis patients admitted to our clinic in the past year. 5 patients, who were admitted to our clinic in the past year and diagnosed with follicular cystitis, are evaluated retrospectively (Table 1).

The mean age of the patients was 54.6 (35-72). 3 of the patients diagnosed with follicular cystitis were males and 2 were females. Male patients were admitted with complaints of hematuria and pollakiuria, with findings of accompanying bladder outlet obstruction. Female patients had complaints of dysuria, with a history of recurring urinary tract infection. In 1 patient, there was hypertension as a comorbid disease. It was learned from the anamnesis of all patients that they received antibiotic treatment for a urinary tract infection diagnosis within the past month, but their complaints did not improve. No findings were detected in their physical examinations. In their tests, the mean amount of white blood cells was 7.22 (5.1-9.5) K/uL, while the mean rate of lymphocytes was 29.6% (17.1-35.6%) and both were considered normal. While the hemoglobin levels of the male patients were at the level of anemia with an average of 12.5 gr/dL, that of the female patients were at 13 gr/dL. While an average of 317 (3-758) erythrocytes were detected in every field in the full urinalysis in male patients, an average of 11 (4-18)

Received: 08.03.2016

Accepted: 04.04.2016

### Corresponding Author

Caner Ediz

Üsküdar State Hospital, Department of Urology,

İstanbul, Turkey

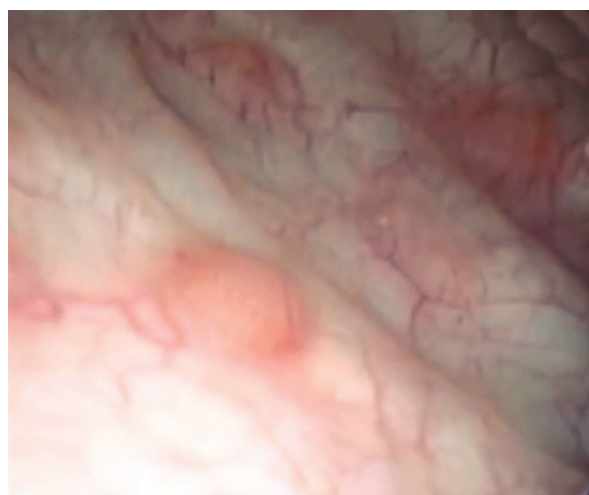
E-mail: drcanerediz@hotmail.com

erythrocytes were detected in female patients. There was no growth in the urinary culture of any patients. In their ultrasonography, the urinary system was assessed normal in 4 patients, while in 1 patient a suspected bladder mass was observed in the bladder. In the cystoscopy of the patients, lesions of nodular character were observed in one patient (Figure 1), white lesions of superficial character with erythematous surface were observed in two patients, a lesion displaying a slightly papillary extension from the bladder surface was observed in one patient and an apparent mass displaying a prominent papillary extension was observed in one patient (Figure 2). All lesions were located in the trigone. Lymphoid follicles showing prominence of the

germinal center in the lamina propria were present in the histopathological examination of cold punch biopsy specimens obtained from the patients (Figures 3-4). In the immunohistochemical analyses, CK7, Ki-67 and p53 were detected as positive (+). An expression with a CD3 and CD20 reactive pattern was observed in the lymphocytes. Ciprofloxacin 750 mg 2\*1 along with etodolac 400 mg 1\*1 were started on all patients when being discharged. Patients were recommended to continue with 3 months of maintenance therapy of a single daily dose of nitrofurantoin after their full dose treatment. In their 3rd month follow-up, it was learned that there was full symptomatic improvement in 4 patients and partial improvement in one.

**Table 1.** Data of follicular cystitis patients

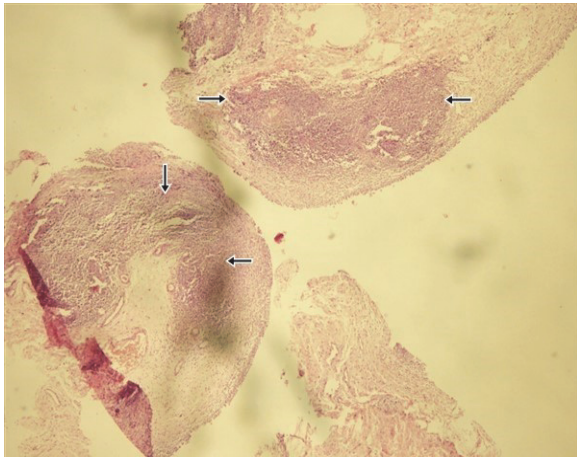
| Patient | Sex    | Age | Disease Period (Months) | Symptoms                                       | Previous Treatment History              | Cystoscopic Findings      | Treatment  |
|---------|--------|-----|-------------------------|--|---|---------------------------|--|
| 1       | Male   | 60  | 3                       | Dysuria, Pollakiuria and Microscopic Hematuria | Cephalosporin (One Week)                | Multiple Nodular Lesions  | Ciprofloxacin 750 mg 2*1<br>Etodolac 400 mg 1*1<br>*Nitrofurantoin 50 mg 1*1<br>(3 Months)                       |
| 2       | Male   | 72  | 5                       | Recurrent Microscopic Hematuria                | Quinolone (One Week)                    | Erythematous Lesions      | Ciprofloxacin 750 mg 2*1<br>Etodolac 400 mg 1*1<br>*Nitrofurantoin 50 mg 1*1<br>(3 Months)                       |
| 3       | Female | 53  | 24                      | Dysuria and Recurrent Urinary Tract Infections | Quinolone or Cephalosporin (Many Times) | Erythematous Lesion       | Ciprofloxacin 750 mg 2*1<br>Etodolac 400 mg 1*1<br>*Nitrofurantoin 50 mg 1*1<br>(3 Months)                       |
| 4       | Female | 35  | 36                      | Dysuria and Recurrent Urinary Tract Infections | Quinolone or Cephalosporin (Many Times) | Slightly Papillary Lesion | Ciprofloxacin 750 mg 2*1<br>Etodolac 400 mg 1*1<br>*Nitrofurantoin 50 mg 1*1<br>(3 Months)                       |
| 5       | Male   | 53  | 4                       | Macroscopic Hematuria                          | Quinolone (One Week)                    | Papillary Lesion          | Surgical Treatment<br>Ciprofloxacin 750 mg 2*1<br>Etodolac 400 mg 1*1<br>*Nitrofurantoin 50 mg 1*1<br>(3 Months) |



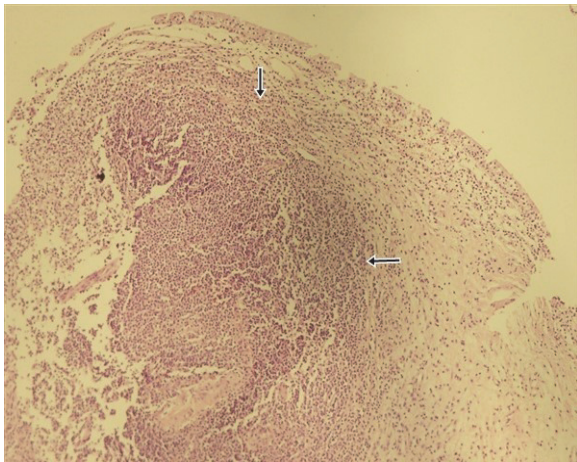
**Figure 1.** A large number of nodular lesions that are slightly raised and erythematous on the surface of bladder.



**Figure 2.** Showing the extension of the papillary lesion on bladder surface.



**Figure 3.** H&E x 40. The bladder mucosa localized lymphoid follicles.



**Figure 4.** H&E x 100. Lymphoid follicle structure in subepithelial area consisting the majority of lymphocytes and plasma cells.

Although its etiology has not been fully revealed, it is known that inflammatory reactions are dominant and that it can follow course with comorbid diseases that can lead to this kind of portrait. Exposure to chronic irritation within the bladder is thought to be important in the etiology. The fact that it is more common in patients with recurrent urinary tract infections and bladder stones as well as those who have undergone chronic catheterization supports this theory. This chronic exposure goes into a reaction with the bladder mucosa, enabling the formation of lymphoid follicles (5). In a study conducted by Marsh et al., follicular cystitis has been observed at a rate of 35% in patients with chronic urinary tract infection (6). In addition, tumoral formations inside the bladder can cause to the development of follicular cystitis by stimulating immunological mechanisms in the surrounding bladder mucosa. In a study conducted by Sarma, this rate was revealed to be 40% in bladder tumor patients (2). Another indicator of immunological activation is the development of follicular cystitis in patients who have undergone intravesical BCG treatment (7). In a study carried out by Giannopoulos et

al., the IFN-gamma delivered into the bladder as a prophylactic to prevent recurrence in patients on follow-up for superficial bladder tumor led to follicular cystitis formation 6 months later (8). Radiotherapy is known to cause urothelial cell and vascular endothelial damage on the bladder surface (9). Aside from a picture of cystitis that has developed due to radiotherapy, cases of radiotherapy related follicular cystitis have also been reported in the literature.

Follicular cystitis leads to nonspecific symptoms in the urinary tract. It usually presents with dysuria, pollakiuria, urgency of urination, microscopic or macroscopic hematuria or suprapubic pain in the lower urinary system. Recurrent urinary tract infection or resistant microscopic or macroscopic hematuria attacks can be present in the history of patients. In addition, irregular use of antibiotics and having immediately resorted to medication in cystitis attacks are also seen commonly in their histories. However, these symptoms and findings are not specific and only ensure suspicion on the part of the clinician. Although the physical examination of patients may generally be normal, nonspecific bladder sensitivity can rarely be observed. Contribution of hemogram or biochemical parameters is very limited in the diagnosis. The presence of leukocytes and erythrocytes emerges frequently in patients as a result of urine analysis. A prominent lymphocytosis formed by lymphocytes that separate from the germinal center of lymphoid follicles can be detected in the urine cytology (4). However, cytology may not always yield accurate results in cases of follicular cystitis (10). Follicular cystitis may also present as a result of histopathological evaluation in cases with detected cellular atypia (11). There is not much place for imaging methods in the diagnosis. Ultrasonography can be meaningful in some cases of follicular cystitis with an appearance of papillary style pseudoneoplastic mass (12). Therefore, imaging methods can make a contribution in the differential diagnosis rather than the diagnosis of patients. The real diagnosis of follicular cystitis consists of cystoscopy planning followed by histopathological examination. In the cystoscopy, mostly the presence of nodules that are pink, white or gray in color with an erythematous surface and trigone localization can be detected. Pseudoneoplastic masses displaying papillary extensions can be confused with bladder tumor. For this reason, diagnosis is made as a result of sampling together with histopathological interpretation. Taking cold punch biopsy samples from suspicious lesions in the bladder or transurethral resection of lesions with papillary mass appearance is necessary in terms of histopathological evaluation. The most remarkable matter requiring attention is the recognition of lymphoid structures of malignant character. While follicular lymphoma takes its place in differential diagnosis, it is seen very rarely in the bladder. Small follicles consisting of small, notched cells without nucleolus (centrocyte) as well as large, unnotched cells with an open chromatin and multiple nucleoli (centroblasts) are observed. Tingible body macrophages and apoptotic bodies are almost never observed and a positive expression is observed in these cells with the bcl-2 indicator. Other non-hodgkin lymphomas consist of monomorphic atypical lymphoid

populations. Granulomas are also similar but they are histiocyte rich formations. Follicle structures do not form in sporadic cystitis and atypia is not observed in the surrounding epithelium. While the cystoscopic appearance of tuberculosis is similar to follicular cystitis, granulomas are histopathologically present (13).

The targeted point in the treatment of follicular cystitis is cause-oriented treatment and the suppression of inflammation. Therefore, antibiotic treatment is suggested to patients. Long term suppressive antibiotic dose or urinary antiseptic use can also be planned in patients with a history of recurrent urinary tract infection. In addition, anti-inflammatory drugs are also routinely used in order to reduce inflammatory reaction. Prednisone treatment and Vitamin A supplementation are other conservative treatment options for the reduction of inflammation. Methods of washing the inner bladder with analgesics, use of local anesthetics and fulguration are minimally invasive treatment alternatives (14). Studies related to intravesical treatment methods such as pentosanpolysulphate and dimethyl sulphoxide are limited, with no clear consensus on the subject of their routine application. While a great majority of patients respond well to conservative treatment methods, some cases can present clinical pictures of resistant follicular cystitis. Radiotherapy, bladder augmentation and cystectomy can be applied, albeit rarely, in such cases (15). In radiotherapy, the administration of 3 consecutive days of 200 cGy, 600 cGy in total, leaving a 1.5 cm bladder margin 3 weeks after surgical procedure has been proposed (16). Palliative cystectomy is the last resort since it is a major surgery that may affect the quality of life. As much as follicular cystitis follows a course together with malign pathologies, prognosis-wise it is extremely harmless and carries no risks of malignant transformation (5).

Follicular cystitis is a cystopathology that is rarely encountered in the practice of urology. Its diagnosis may take time because its cause is not entirely known and, therefore, there is no identified specific treatment. Follicular cystitis should be considered in particular in patients past their 50s with recurrent hematuria and urinary tract infections. Although, in terms of diagnosis, there is no specific method available, cystoscopy followed by histopathological examination is the most accurate method to eliminate clinical suspicion. Molecular and genetic studies with large series are needed to help us better understand the course of the disease.

## REFERENCES

1. Mateos BJ, Lallave Martín F. Follicular cystitis. Case report and bibliographic review. *Arch Esp Urol* 2007;60(1):77-80.
2. Sarma KP. On the nature of cystitis follicularis. *J Urol* 1970;104:709.
3. Sternberg S, Mills S. *Diagnostic Surgical Pathology* (5th edition). Philadelphia, Pa: WoltersKluwer/Lippincott Williams &Wilkins; 2010.
4. Zaharopoulos P. Cytologic manifestations of cystitis follicularis in urine specimens *Diagn Cytopathol* 2002;27(4):205-9.
5. Domínguez Freire F, Núñez López A, Alonso Rodrigo A. A case report and review of the literature. *Actas Urol Esp* 2003;27(7):551-4.
6. Marsh FP, Banerjee R, Pancharia P. The relationship between urinary infection, cystoscopic appearance and pathology of the bladder in man. *J Clin Pathol* 1974;27(4):297-307.
7. El-Sayed Ali Z, Rosenthal DL, Ali TZ. *Atlas of urinary cytopathology: with histopathologic correlations. nonneoplastic Lesions-Reactive Conditions* 2010;3:49.
8. Giannopoulos A, Constantinides C, Fokaeas E. The immuno modulating effect of interferon-gamma intra vesical instillations in preventing bladder cancer recurrence. *Clin Cancer Res* 2003;15;9(15):5550-8.
9. Anthony Kanai, Michael Epperly, Linda Pearce, et al. Differing roles of mitochondrial nitric oxid esynthase in cardiomyocytes and urothelial cells. *Am J Physiol Heart Circ Physiol* 2004;286:13-21.
10. Okamura K, Ito K, Suzuki Y. Histological study of cases of bladder cancer and chronic cystitis with difficulty in cystoscopic diagnosis. *Hinyokika Kyo* 1984;30(4):459-65.
11. Siddappa S, Mythri KM, Kowsalya R. Cytological findings in routine voided urine samples with hematuria from a tertiary care center in south India. *J Cytol* 2012;29(1):16-9.
12. Duarte Novo JE, Patiño ML, Ruibal Moldes M, et al. Follicular cystitis. Presentation as bladder pseudotumor. *Actas Urol Esp* 1998;22(1):67-9.
13. Varo Solís C, Bachiller Burgos J, Báez JM. Glandular cystic cystitis. *ActasUrolEsp* 2000;24 (7):594-8
14. Hansson S, Hanson E, Hjälmås K. Follicular cystitis in girls with untreated asymptomatic or covert bacteriuria. *J Urol* 1990;143(2):330-2.
15. Graham S, Keane T. *Glenn's Urologic Surgery* (7th edition). Philadelphia, PA: WoltersKluwer/Lippincott Williams &Wilkins; 2009.
16. Trombetta M, Packard M, Ferrara D. The use of radiotherapy in the management of follicular cystitis refractory to conservative and surgical management. *Rare Tumors* 2012;12;4(2):e25.