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# Original Article

# The Diagnostic Value of Serum IgG-Antigliadin, IgA Anti-endomysial and IgA Anti-tissue Transglutaminase Antibodies for Pediatric Celiac Disease

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## ABSTRACT

***Background and Objective:*** **Celiac disease is an autoimmune disorder, characterized by inflammation, villous atrophy, and crypt hyperplasia of the small bowel mucosa. In this study we considered and compared sensitivity and specificity of serological tests in patients with celiac disease.**

***Materials and Methods:*** **In this cross-sectional study we prospectively recruited children with suspected celiac disease. An intestinal biopsy specimen was obtained from all patients. Celiac disease diagnosed on the basis of histologic findings of Marsh classification. A serum sample was taken at the time of biopsy for serologic tests. Findings were analyzed using SPSS program, t-test, and chi-square tests.**

***Results:*** **Out of a total of 134 children in this study, seventy (52.21%) patients were boy and sixty four (47.8%) patients were girl. Celiac disease was diagnosed in 14 (10.4%) of the patients. In serologic tests, 11 patients (78.6%) were positive for antigliadin-Ab, 4 (28.6%) for anti tissue-transglutaminase Ab, and 9 (64.3%) for antiendomysial antibody. Sensitivity of antigliadin-Ab was 78.6% and its specificity was 95.9%. Sensitivity of anti tissue-transglutaminase Ab was 28% and its specificity was 95%. Sensitivity of antiendomysial Ab was 64% and its specificity was 96%.**

***Conclusion:*** **Positive serologic tests are supportive of the diagnosis in those with characteristic histopathologic changes on small intestinal biopsy. The best tests for this purpose are the IgA antiendomysial antibody or IgA anti tissue-transglutaminase, both of which are highly sensitive and specific.**

**Key words: Celiac Disease, Gliadin, Transglutaminases, Antibodies**

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## Introduction

Celiac disease or gluten-sensitive enteropathy is an autoimmune disorder characterized by inflammation, villous atrophy, and crypt hyperplasia of the small bowel mucosa. The mucosal lesion develops in genetically susceptible individuals after ingestion of dietary gluten and recovers when gluten-containing cereals, wheat, rye, and barley are withdrawn from the diet (1). The disease should be detected as early as possible, because untreated celiac disease is associated with many severe complications such as intestinal lymphoma or cancer and osteoporesis (1-2). In untreated celiac disease, the characteristic abnormalities in the small bowel mucosa are villous atrophy, crypt hyperplasia, and an increased density of inflammatory cells in the epithelium and lamina propria. This type of lesion is nowadays uncommon in other conditions (3). The mucosal lesion recovers with a gluten-free diet and deteriorates further if the patient resumes a gluten-containing diet (1). The occurrence of circulating antibodies against gliadin or intestinal matrix further supports a diagnosis of celiac disease.

Various antibody assays have been developed to select patients for diagnostic small-bowel biopsy. Anti-reticulin and anti-gliadin antibodies (AGA) were the first tests to be employed in screening, the latter still being widely in use. In the context of celiac screening in asymptomatic patients and in various risk groups, however, the benefits of the more recent IgA class anti-endomysial antibody test (EMA-Ab) and the latest anti tissue-transglutaminase test (TTG-Ab) would now seem obvious (4).

In this study, we evaluated and compared sensitivity and specificity of these tests in patients with diagnosed celiac disease (CD).

## Materials and Methods

In this cross-sectional study, from January 2006 to January 2008 we prospectively recruited children with suspected celiac disease who were referred to the division of Pediatric Gastroenterology at a pediatric hospital in Tehran (134 children). Presenting symptoms generally included failure to thrive (FTT), chronic diarrhea, abdominal distention, and steatorrhea. Patients were included if the intestinal biopsy was positive and if serologic tests were positive. Patients were excluded if pathology report of intestinal biopsy was negative or serologic tests were all negative or had been on a gluten- free diet. An intestinal biopsy specimen was obtained from all patients. At least 2 distal duodenal biopsy specimens, adequate in size and orientation, were examined by two experienced pathologists, blind to the serologic tests results. Celiac disease was diagnosed on the basis of histological findings of Marsh classification. A serum sample equal to 5-7 ml was taken at the time of biopsy and stored at -70 °C until testing for AGA, EMA-IgA and TTG-IgA. All antibodies were measured by immunometric enzyme immunoassay method using kits for in vitro diagnostic use (Orgentec diagnostica). Each run was checked against stated quality control requirements. Sensitivity or the lower detection limits for anti TTG-IgA and anti EMA-IgA were determined at 1.0 u/ml and for anti gliadin IgG were determined at 0.5 u/ml. Findings of pathologic examinations, serologic tests, gender, age, and family history, and clinical presentation were analyzed using SPSS program (version 11.5), and t test and chi-square tests.

## Results

In this study, out of a total of 134 children, seventy patients were boy (52.2%) and sixty four patients were girl (47.8%). Celiac disease was diagnosed in 14 (10.4%) of the patients. Seventy nine of the patients were aged below six (58%). They included 42 girls (53.1%; five with positive celiac and thirty seven with negative celiac) and 37 boys (46.9%; four with positive celiac and thirty three with negative celiac). Fifty five (42%) patients belonged to the 6-12-years-old age group. They included 22 girls (three celiac-positive and 19 celiac-negative). Out of 134 examined children, 114 (85.1%) suffered from chronic diarrhea, 57 (42.5%) from steatorrhea, 114 (89.6%) from FTT, the entire 14 celiac-sufferer children, all (100%) had chronic diarrhea, 9 (64.3%) from steatorrhea, and 13 (92.9%) from FTT. Out of 134 cases, 12 (9%) had a family record of the disease and among celiac sufferers (14 children), one (7.1%) had a positive family record. Regarding stool exam tests carried out on 134 diagnosed patients, 49 (36.6%) had fatty drop and the average pH for the stool was 0.44 and SD = 5.59. In addition, 10 cases (71.4%) out of 14 patients

that suffered celiac had fatty drop on stool exams with average stool pH equal to 0.44 and SD = 5.22.

In serologic tests, 16 patients (11.9%) was positive for anti-gliadin antibody, 10 patients (7.5%) for TTG-Ab, and 14 patients (10.4%) for EMA-Ab. In addition, 11 (78.6%) cases out of 14 patients that suffered from celiac were positive for anti-gliadin antibody, 4 (28.6%) patients were positive for TTG-Ab, and 9 (64.3%) were positive for EMA-Ab. Meanwhile, 20 cases (14.9%) out of 134 patients were positive following small intestinal biopsy. Sensitivity of AGA test was 78.6% and its specificity was 95.9%. Sensitivity of TTG-Ab test was 28% and its specificity was 95%. Sensitivity of EMA-Ab was 64% and its specificity was 96%.

## Discussion

The results of the past studies have shown that the EMA-IgA and the human recombinant TTG-IgA are the most sensitive and specific serologic tests for identifying individuals who need to undergo an intestinal biopsy examination to diagnose CD (5-11). For the EMA-IgA test, the majority of studies report a sensitivity in excess of 95% and all but 1 study found the specificity to be in excess of 95% (5-11) (Table 1). In our study, the sensitivity and the specificity stand respectively at 64 and 96 percent. The specificity is close to one, but the inconsistency between the sensitivities might be related to the difference in the volume of samples or the sensitivity of kits or the difference in the stage of disease.

**Table 1: Sensitivities and specificities for the EMA-IgA test**

| Author | Date | Age group | Sensitivity(%) | Specificity(%) |
|---|---|---|---|---|
| Bonamico et al[5] | 2001 | Children | 95 | 98 |
| Delecea et al[6] | 1996 | Children | 88 | 90 |
| West et al[7] | 2002 | Adults | 94 | 100 |
| Tesei et al[8] | 2003 | Adults | 86 | 100 |
| Carroccio et al[9] | 1996 | Children | 97 | 100 |
| Bugin-walkff et al[10] | 1991 | Children | 90 | 98 |
| Dileo et al[11] | 1999 | Children | 100 | 97 |

An initial review of the data for TTG-IgA might suggest it is less sensitive and specific than the EMA-IgA (5, 12-15), but direct comparison between the human recombinant TTG-IgA and the EMA-IgA failed to show any significant differences (12, 16-18) (Tables 2-3). In our study, the sensitivity and the specificity stand respectively at 28 and 95 percent. The specificity is close to one, but the inconsistency between the sensitivities might be related to the difference in the volume of samples or the sensitivity of kits or the difference in the stage of disease. For these different sensitivities, it is suggested that the study be conducted with one more sample and a specific criterion for diagnosis of the disease and the consistency between Abs titers and the stage of the disease.

**Table 2: Sensitivities and specificities for the TTG-IgA test**

| Author | Date | Age group | Sensitivity(%) | Specificity(%) |
|---|---|---|---|---|
| Bonamico et al[5] | 2001 | Children | 90 | 100 |
| Dickey et al[12] | 2001 | Adults | 77 | 98 |
| Vitoria et al[13] | 1994 | Mixed | 61 | 91 |
| Ascher et al[14] | 1996 | Mixed | 91 | 98 |
| Leon et al[15] | 2001 | Not Stated | 99 | 99 |

**Table 3: Studies comparing EMA-IgA and TTG-IgA**

| Author | Date | EMA-IgA | | TTG-IgA | |
|---|---|---|---|---|---|
| | | Sensitivity(%) | Specificity(%) | Sensitivity(% ) | Specificity(%) |
| Bonamico et al[12] | 2001 | 95 | 98 | 90 | 100 |
| Baldas et al[16] | 2000 | 93 | 100 | 100 | 98 |
| Sulkanen et al[17] | 1998 | 93 | 99 | 95 | 91 |
| Sblaterro et al[18] | 2000 | 93 | 100 | 98 | 99 |

The sensitivities and specificities for the AGA tests were not only highly variable but generally were lower than those for the EMA-IgA and TTG-IgA (9-10, 19-20). For the AGA-IgG, most studies reported a sensitivity of less than 90%, whereas the specificity was below this level for all of the samples (21). Specificity for the AGA-IgA was better than that for the AGA-IgG, with the majority of studies reporting levels of 90% or more, but the sensitivity was poor (9-10, 19-20) (Table 4). In our study, the sensitivity and the specificity stand respectively at 78.6 and 95.9 percent.

**Table 4: Sensitivities and specificities for the AGA-IgG test**

| Author | Date | Age group | Sensitivity(%) | Specificity(%) |
|---|---|---|---|---|
| Wolters et al[19] | 2002 | Not stated | 83 | 80 |
| Carroccia et al[9] | 1996 | Children | 89 | 72 |
| Burgin-wolff et al[10] | 1991 | Children | 89 | 65 |
| Lerner et al[20] | 1994 | Children | 88 | 92 |

Based on these findings, either the EMA-IgA or TTG-IgA test is best suitable to identify those individuals who require an intestinal biopsy examination to diagnose CD while avoiding an unnecessary biopsy examination in those who do not have the condition. Because of the variable and generally lower sensitivity and specificity associated with the AGA, these tests are less suitable for screening purpose there are no data to show that a combination of tests is better than a single test using either EMA-IgA or TTG-IgA (21-22).

There have been no other studies that specifically evaluated whether the performance of the serologic tests varied in different racial or ethnic groups. With regard to age group difference, the past data suggest the AGA-IgG may be more sensitive in children compared with adults. There was no clear difference between children and adults for the AGA-IgA test.

## Conclusion

In clinical practice, serologic tests for CD are frequently used to identify both symptomatic and asymptomatic at-risk individuals who require an intestinal biopsy examination to confirm the diagnosis. A positive test is also supportive of the diagnosis in those with characteristic histopathology change on small intestinal biopsy examination. Based on our study, the best tests for this purpose are the EMA-IgA or TTG-IgA, both of which are highly sensitive and specific.

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# Original Article

## Inflammatory Pseudotumor of the Orbit: A Histopathologic and Immunohistochemical Study of 32 Cases

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### ABSTRACT

***Background and Objective:*** **Inflammatory pseudotumor is a lesion composed of proliferating spindle cells with mixed inflammatory infiltrates. Some authors have proposed the name inflammatory myofibroblastic tumor as a proper descriptive term rather than the vague inflammatory pseudotumor. The aim of this study was to verify the myofibroblastic origin of spindle cells in idiopathic orbital inflammatory pseudotumor by immunohistochemical staining.**

***Materials and Methods:*** **We reviewed a series of 32 inflammatory pseudotumors arising in orbit for expression of smooth muscle actin, vimentin, desmin and anaplastic lymphoma kinase using immunohistochemical staining.**

***Results:*** **There were 21 females and 11 males aged 3 to 64 years with a mean age of 31.**

**Immu-nohistochemically, spindle cells of 51.75%, 79.3%, and 17.2% of lesions expressed smooth muscle actin (15/29), vimentin (23/29) and desmin (5/29). All lesions (32/32) were negative for anaplastic lymphoma kinase**

***Conclusion:*** **In this study, reactivity for smooth muscle actin in spindle cells can be demonstrated as myofibroblastic differentiation. The absence of anaplastic lymphoma expression in all cases of orbital inflammatory pseudotumor in this study strongly suggests that these lesions, albeit histologically similar, are biologically distinct from their soft tissue counterparts or those inflammatory myofibroblastic tumor that negative for anaplastic lymphoma immunoreactivity may be characterized by one or more chromosomal aberration involving regions other than 2p23 is as yet unknown.**

**Key words: Inflammatory pseudotumor, Orbit, ALK kinase**

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## Introduction

Idiopathic inflammatory pseudotumor (IPT) of the orbit or eye is a rare, benign and self-limited disorder (1-4). These tumors most commonly arise in the lungs and abdomen, but they have been reported in virtually all anatomic subsets of the body in patients of all ages (5). In the head and neck, the orbit is the most common site of occurrence (5). Its pathogenesis is unknown.

The diagnostic entity "inflammatory pseudotumor" has undergone something of a revolution in recent years. What was once a heterogeneous group of poorly defined entities has been refined, and it presently encompasses several distinct biologic processes including both reactive condition as well as neoplasm (6-9). Some authors have proposed the name ''inflammatory myofibroblastic tumor'' as a proper descriptive term for this tumor, rather than the vague ''inflammatory pseudotumor. Inflammatory myofibroblastic tumor (IMT) is a lesion composed of proliferating myofibroblastic spindle cells with mixed inflammatory infiltrates of lymphocytes, plasmacells, eosinophils and histiocytes (10).

Histopathologic discrimination of these lesions may require careful attention not only to the histopathologic findings but also to clinical course and to additional diagnostic tools, particularly immunocytochemistry. The neoplastic nature of IMT was confirmed by proving the presence of clonal abnormalities in the short arm of chromosome2 (2;3;6-8) involving the anaplastic lymphoma kinase (ALK) gene. Resultant ALK protein over-expression in myofibroblastic cells was found out in 35% to 60% of IMT cases, suggesting neoplastic nature of these tumors rather than a reactive or reparative process (6-8). However, the concept of the same lesions in orbit was not changed and was still referred to as "inflammatory pseudotumor" (IPT) but in a few case reports used term "inflammatory myofibroblastic pseudotumor" when myofibroblasts were rich in the mass. We consider that they are the same lesion that occurs in the other soft tissue and suggest that they be referred to in unison as IMT.

To verify the histopathology and immunohistochemistry for myofibroblastic differentiation and ALK expression of orbital IPT, we analyzed clinicopathologic features and performed SMA, vimentin, desmin and ALK immunohistochemistry on 32 cases of orbital IPT.

## Materials and Methods

Thirty two cases of orbital inflammatory pseudotumor were selected from the histopathology files of the Department of Pathology at the Farabi hospital between 1991 and 2007. Clinical information (age and sex of the patient, site and side of the lesion) was obtained from the pathology report.

Hematoxylin and Eosin-stained slides were reviewed in all cases. All cases met the established light microscopic histopathologic criteria for orbital inflammatory pseudotumor (11). Formalin-fixed, paraffin-embedded sections were available in all cases. Immunohistochemical staining was performed using a conventional labeled stereptavidin-biotin method according to the manufacturer's protocol. Briefly, 4 μm tissue sections were placed on silanecoated slides, deparaffinized, and rehydrated with graded ethanol and phosphate-buffered saline. After antigen retrieval by microwaves blocking endogenous peroxidase, goat serum to prevent nonspecific reaction and primary antibodies were applied sequentially. The primary antibodies (Table 1) used were as follows: SMA (n = 29; DAKO, dilution 1:100), vimentin (n = 29; DAKO, dilution 1:100), desmin (n = 29; DAKO, dilution 1:100) and ALK-1 protein (n = 32; DAKO, dilution 1:250). These slides were incubated in biotinylated goat anti-mouse immunoglobulin and then in a solution of stereptavidin-biotin complex. Immunoreactivity was visualized using 3,3-diaminodenzidine (DAB).

Reaction was interpreted as positive if a distinct precipitate was present in cytoplasm of the spindle cells. The positive control for ALK-1 was an anaplastic large cell lymphoma, which showed a diffuse cytoplasmic positivity. Positive reaction of α-SMA with or without vimentin or desmin was considered as myofibroblastic differentiation.

**Table 1: Immunohistochemical antibodies**

| Antigen retrieval | Dilution | Source | Antibody (clone) |
|---|---|---|---|
| Microwave | 1:100 | DAKO | SMA |
| Microwave | 1:100 | DAKO | Vimentin |
| Microwave | 1:100 | DAKO | Desmin |
| Microwave | 1:250 | DAKO | ALK-1 |

## Results

**Clinical features**

The patients' mean age was 31 years (ranging from 3 to 64 years) and females were affected more often than males (1.9/1). Tumor side varied and included the right (n = 15, 46.9%) and left (n = 17, 53.1%). The most common presentation was proptosis followed by pain and swelling.

**Gross and microscopic findings**

The lesions were unilateral (n = 30) or bilateral (n = 2) ranging in size from 0.3 to 4 cm (mean 1.37 cm) and having gray-white to creamy-brown color. Microscopically, all cases were composed of spindle cells, a variable fibrocollageneous stroma, and inflammatory cells component made up lymphocytes, plasmacells, histiocytes, neutrophils and eosinophils. The proportion of each of these elements varied between cases, as well as within cases. Other histopathological findings including perivascular lymphocytic infiltration, fat necrosis, lymphoid follicle formation myositis and dacryoadenitis variably were also seen in some cases. The spindle cells had a long and eosinophils cytoplasm without cross-striation (Fig. 1). Mitosis and coagulative necrosis was not present. Type of lesions is summarized in Table 2.

**Table 2: Type of idiopathic orbital inflammatory pseudotumor**

| Type | Frequency | Percent (%) |
|---|---|---|
| Acute | 3 | 9.4 |
| Subacute | 13 | 40.6 |
| Chronic | 15 | 46.9 |
| Chronic sclerosing | 1 | 3.1 |

**Immunohistochemical findings**

The spindle cells were immunoreactive for alpha smooth muscle actin (SMA) in 15 out of 29 cases (Fig. 2) and vimentin in 23 out of 29 cases, 51.7% and 79.3%, respectively. Thirty two out of 32 cases studied were negative for the ALK-1 protein (Table 3).

**Table 3: Antibodies and immunohistochemical results**

| Antibody | Number of stained cases | Percent of positive test (number) |
|---|---|---|
| SMA-α | 29 | 51.7% (15) |
| Vimentin | 29 | 79.3% (23) |
| Desmin | 29 | 17.2% (5) |
| SMA & Vimentin-α | 29 | 44.8% (13) |
| SMA & Desmin-α | 29 | 6.9% (2) |
| SMA & Desmin & Vimentin-α | 29 | 3.4% (1) |
| Desmin & Vimentin | 29 | 17.2% (5) |
| SMA or vimentin | 29 | 86.2% (25) |
| ALK | 32 | 0% (0) |

Comparison of immunohistochemical results in different microscopic types of orbital inflammatory pseudotumor is summarized in Table 4.

**Table4: Comparison of immunohistochemical results in different microscopic types of idiopathic orbital inflammatory pseudotumor**

| Type | Frequency | SMA | Vimentin | Desmin | SMA & Vimentin |
|---|---|---|---|---|---|
| Acute | 3 | 2 (50%)/1 | 1/2 (50%) | 0/1 (0%) | 1/2 (50%) |
| Subacute | 13 | 8/13 (61.5%) | 9/13 (69.2%) | 1/13 (7.7%) | 6/13 (46.2%) |
| Chronic | 15 | 6/13 (46.2%) | 12/13 (92.3%) | 3/13 (23.1%) | 6/13 (46.2%) |
| Chronic sclerosing | 1 | 0/1 (0%) | 1/1 (100%) | 1/1 (100%) | 0/1 (0%) |

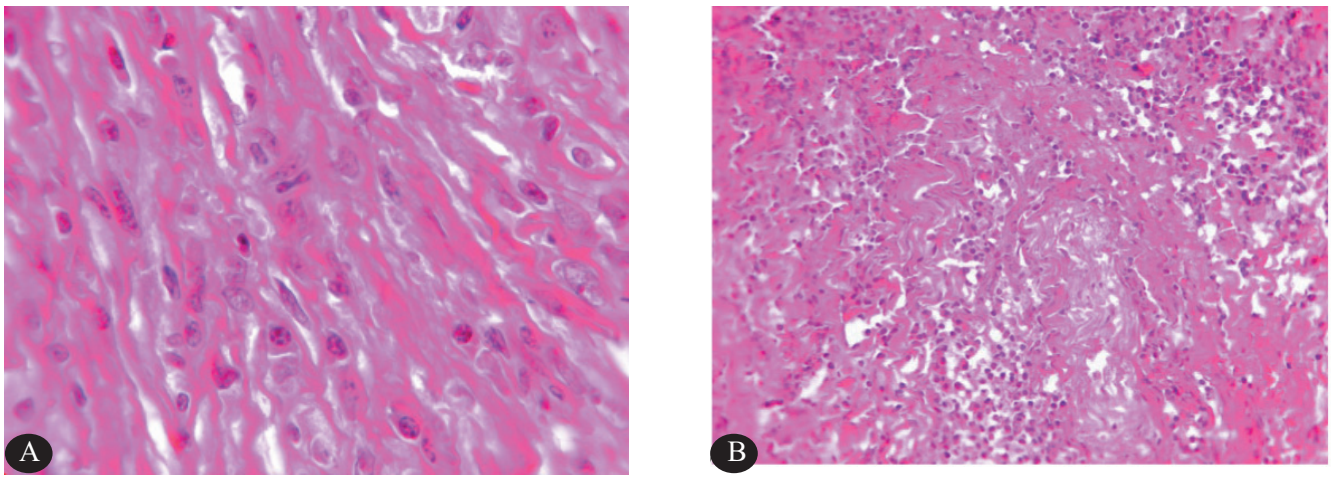


**Fig.1: (A & B) inflammatory pseudotumor of orbit. The lesion composed of spindle cells admixed with inflammatory infiltrated cells (×100 & ×400).**

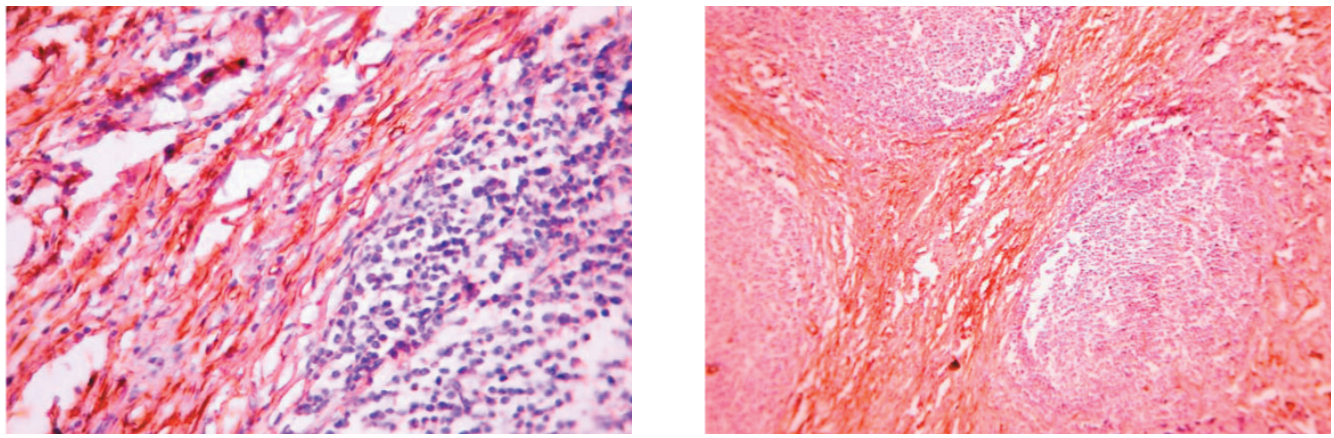

**Fig .2. Spindle immunoreactivity for SMA (smooth muscle actin) (Avidin-biotin peroxidase; ×100 & ×400). Note the follicle formation of inflammatory cells.**

## Discussion

Despite many studies, the nature of IPT has remained a curious lesion. It was originally described in the lung and called plasmacell granuloma (12). The term inflammatory myofibroblastic tumor commonly referred to as inflammatory pseudotumor in the earlier literature (13) and implies for myofibroblastic differentiation, which is supported by immunohistochemical and ultrastructural data. IMT is a neoplastic process that can arise in many sites within the head and neck including orbit (14-16). The histological features of this tumor vary slightly from site to site, which may at least in part, be related to the differences in the phase of the lesion's development at the time the lesion becomes symptomatic or detectable. The histopathologic examination is essential to the diagnosis of IMT. Microscopically, IMTs are composed of proliferating spindle cells, a variably

prominent collagenous stroma and a background of inflammatory cells consists mainly of lymphocytes and plasma cells. Immunohistochemical staining is useful in confirmation of the myofibroblastic phenotype (17-20).

Our immunohistochemical findings for myofibroblastic differentiation are similar to other authors (8;21-29). Immunohistochemically, most of the spindle cells showed evidence of myofibroblastic differentiation, as 15/29 cases stained for smooth muscle actin and 23 out of 29 cases stained for desmin, in contrast to the findings of Facchetti et al that most spindle cells were positive for vimentin and macrophages-associated markers (30) and by Selves et al that is derived from follicular dendritic reticulum cells (FDRC) (31). Some IMTs may exhibit aggressive local behavior and rarely metastasis (32) and some of them do not respond to conventional treatments (corticosteroids) which point to the possibility that at least some subsets of IMTs are in fact true neoplasm (6;7).

Recent cytogenetic and molecular studies have identified abnormalities of chromosome 2p23 (short arm of chromosome 2 at the region p21-p23, the site of the ALK gene that codes for a tyrosin kinase receptor) (7;33-36). In IMTs immunohistochemistry for ALK-1, P80 is useful as an indicator of 2p23 abnormality and the sensitivity of both antibodies are known to be comparable (8). ALK immunoreactivity has been reported in 36% to 60% of IMT (7;8;14;26;29;33;36;37). ALK-1 reactivity lends support to the diagnosis of IMT and its neoplastic feature. Thirty two cases of orbital IPT were obtained from our files. Immunohistochemistry for ALK receptor kinase expression did not detect ALK kinase expression (0 out of 32). This finding is in sharp contrast to that of Lawrence et al (34) who showed strong ALK kinase expression by immunohistochemistry in 7 out of 11 cases of soft tissue IMT, Coffin et al (7) who reported 12 out of 45 cases of IMT positive for ALK kinase and other studies (7;8;14;26;29;33;36;37). Further support for the absence of ALK expression in some IPTs comes from a study by Neuhauser et al who found no ALK expression in 10 out of 10 cases of splenic IPT (23), Jeffery et al that none of their 13 cases of splenic and lymph node IPT showed ALK expression (38) and other studies (18). Several studies have proposed a role for EBV (23;39) and HHV8 (39;40). One of two case reports of orbital IMT shows ALK expression (28) and another study shows no immunoreactivity for ALK (18). So, the absence of ALK expression in all cases of orbital IPT in this study and most others orbital IMT studies strongly suggests that these lesions, albeit histologically similar, are biologically distinct from their soft tissue and should be considered histopathologic and clinical information and those IMTs that are negative for ALK immunoreactivity may be characterized by one or more chromosomal aberration involving regions other than 2p23 is as yet unknown ounterparts.

## Conclusion

Although ALK immunoreactivity clearly dose not distinguish between a reactive and a neoplastic process, it is possible that FISH analysis for ALK gene alternation might be useful in distinguishing those lesions that are truly neoplastic from those that are reactive.

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# Case Report

## Ureteral Endometriosis: A Report of Two Cases

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### ABSTRACT

**Endometriosis is the presence of benign endometrial glands and stroma outside the uterus. Urinary system involvement by endometriosis is a rare occurrence accounting for only 1.5 % of all endometriosis cases.**

**Case 1. The patient was a 41 years old woman admitted for right flank pain. The physical and gynaecologic examination was unyielding. Intravenous urography (IVU) revealed stenosis in distal part of right ureter, unfortunately associated with hydronephrosis. Case 2. A 26 years old woman who suffered from colic pain in low abdomen and pelvis. The only positive finding was microscopic hematuria. Abdominal sonography showed hydronephrosis of right kidney and proximal part of ureter. Ureterolysis by an open surgical procedure performed for both patients and histologic examination revealed endometriosis of ureter.**

**Endometriosis of ureter is mainly asymptomatic and unfortunately ends in functionless kidney due to prolonged hydronephrosis. Early diagnosis needs high index of suspicion and intended use of paraclinic aids to save patients normal renal function. An individualized therapy plan depending on the patient's age and the extent of the endometriosis should be attempted.**

**Key words: Endometriosis, Ureteral Obstruction, Hydronephrosis**

### Introduction

Endometriosis is defined as the presence of endome-trial glands and stroma outside the uterus and is the second most common pelvic pathology in females (1). It is most commonly diagnosed in women at child-bearing age, with a peak age of 40 to 44 years (2). It can also occur in menopautic women if taking exogenous estrogen or during increased endogenous production of estrogen from the adrenals or pituitary gland. The most common sites of involvement are ovaries, fallopian tubes, rectovaginal septum, and pelvic peritoneum and cul-de-sac in the order of decreased frequency. In addition, it has also been described in the skin, lungs, diaphragm, gastrointestinal tract (colon), laparotomy incision site, umbilicus, obturator nerve and axillary lymph nodes (3). Involvement of the genitourinary tract has been reported at an incidence of 1.5%, with

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peak age incidence at 30 to 35 years (4). The ratio of bladder-to-ureteral-to-urethral involvement is 40:5:1 (5). In a review of 147 patients with endometriosis, Abeshouse and Abeshouse noted that involvement of the bladder, ureter, kidney and urethra to be 85%, 10%, 4% and 2% respectively (6).

Ureteral endometriosis is a rare entity and its diagnosis requires a high index of suspicion. Cullen described the first case of endometriosis causing obstructive uropathy in 1917(7). Since then, more than 200 cases of ureteral obstruction due to endometriotic implants have been described in the medical literature, but the actual prevalence of this condition is difficult to determine. Because of its association with silent renal obstruction, up to 47% of patients will require nephrectomy at the time of diagnosis (8). Most reported cases are unilateral. However, endometriosis involving both ureters has described in patients with more extensive pelvic disease (9). Ureteral endometriosis is more commonly observed in the distal segment of the left ureter. The close anatomical proximity of the distal ureter to the female reproductive organs makes it an ideal target for the development of extrinsic compression of the ureter. To date, only 1 known case of mid-ureteral endometriosis has been reported, and endometriosis affecting the proximal ureter has not been previously noted (10).

## Case reports

**Case report 1**

The patient was a 41 years old woman admitted for right flank pain. The gynaecologic examination was unyielding. Imaging study (sonography, IVU and pelvic CT scan) revealed stenosis in distal part of right ureter associated with hydronephrosis (Fig1). The patient planned for cystoscopy and ureter stenting but the ureteral sond of ureteroscope failed to go up more than 6 cm, so surgery with right Gibson incision was performed. The ureter was obstructed 4-6 cm above the bladder. The stenotic region resected with a safe margin because of the fear of malignancy and anastomosis carried out by Psoas Hitch method. The pathology examination revealed dilated glandular structures with cuboidal linings along with foci of endometrial stroma and hemorrhage mainly in subserosa and muscular coatings of ureter wall. Ureter stent removed 4 weeks after surgery.

**Case report 2**

A 26 years old woman came to visit with a complaint of right flank pain. The physical and gynaecologic examination and all laboratory workups were normal except for microscopic hematuria reported in previous urine analysis. Ultrasonography showed right kidney hydronephrosis. CT scan and IVU revealed stenosis of distal portion of right ureter. The patient planned for surgery; after opening by Gibson incision and resection of stenosis, anastomosis performed by Psoas Hitch method. The histologic examination of the submitted specimen confirmed ureteral endometriosis characterized by endometrial glands and stroma located in outer half of ureter wall which extends to submucosa (Fig. 2). The patient discharged in good health condition and ureter stent removed after 4 weeks.

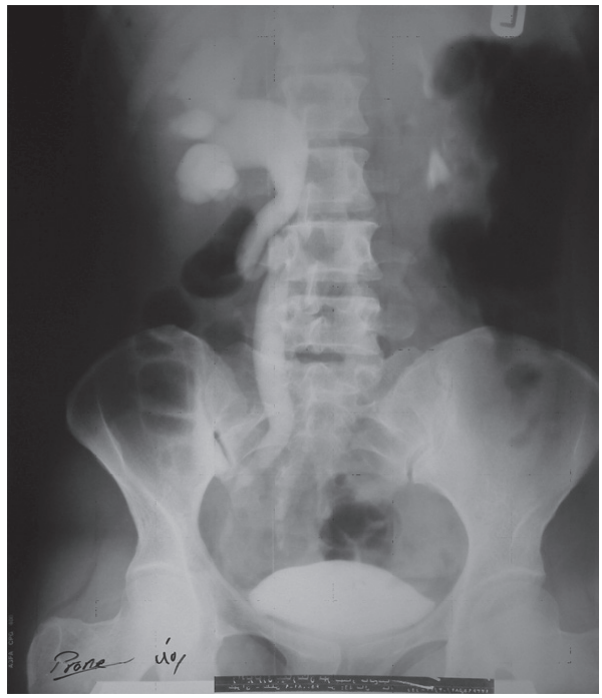

**Fig. 1: The right kidney shows hydronephrosis and the ureteral obstruction is visible above the bladder**

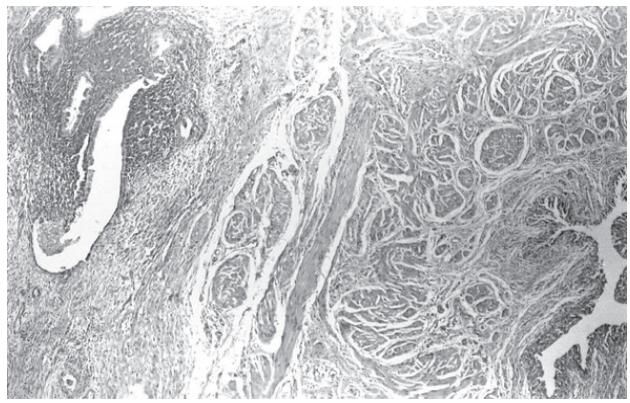

**Fig. 2: The histologic examination revealed endometrial glands and hemorrhage in subserosa of ureter (H&E Staining ×100)**

## Discussion

Ureteral endometriosis is categorized into two groups as extrinsic and intrinsic. The extrinsic one is more common and constitutes more than 80% of reported literature. The serosa is the sole site of involvement in this type (11). The internal type is less common in which the submucosa is the main site of involvement. The distinction of extrinsic or intrinsic nature of ureteral involvement may be somewhat arbitrary, since the depth of invasion in the extrinsic form is seldom histologically corroborated and the differentiation could not be reliably made (12). Combined external and internal endometriosis of ureter are also seen and either type may or may not present with other foci of endometriosis (12).

The pathophysiology of endometriosis is unclear, more so with ureteral involvement than other sites of endometriosis. Several presumed mechanisms are “direct transfer “of endometrial tissue (5;6;13) lymphatic or even hematogenous spread or metaplastic transformation of Mullerian and Wolffian duct remnants. Some evidences such as previous history of pelvic surgery supports the theory of direct transfer (5). Rock and Markham have also postulated the immunologic mechanisms as a cause for endometriosis at least in some cases (13). Although all the proposed theories are feasible, more than one mechanism may be responsible for the development of ureteral endometriosis in a single patient.

Sign and symptoms of ureteral endometriosis are related to the site and degree of obstruction. Ureteral endometriosis can be associated with the classic gynecological symptoms secondary to endometriosis or urological symptoms directly related to the effect of endometrial tissue on the ureter; although, it is more commonly asymptomatic. The classical common presentations of pelvic endometriosis are dysparunia, dysmenorrhea, pelvic pain and menorrhagia. The incidence of hematuria in patients with ureteral endometriosis is 15% (8). Periodic hematuria, historically regarded as the classic symptom of endometriosis involving the genitourinary tract is commonly seen with intrinsic but also rarely reported with extrinsic ureteral endometriosis (9;13). Acosta et al have reported endometriosis mimicking sigmoid carcinoma associated with ureteral obstruction and hypertension (14).

Several paraclinical tests are used for confirmation of ureteral endometriosis depending on the presenting symptom of patient. Ureteroscopy, transluminal sonography, laparoscopy, CT-scaning, IVP and pelvic sonography are among the most useful diagnostic modalities. The role of laparoscopy limited to peritoneal and cul-de-sac endometriosis. The best test for internal type ureteral endometriosis is IVP. Intrinsic endometriosis creates a filling defect within the lumen of the ureter, thereby mimicking numerous urological conditions such as radiolucent stones and transitional cell cancer. In addition, IVP provides information regarding renal function and degree of obstructive uropathy. IVP remains a valuable diagnostic tool for ureteral endometriosis, however, the definitive diagnosis of this disease entity will rely on histologic examination of biopsy material of the lesion (5). CT scan also yields equal results and can be used for estimation of the grade of ureter obstruction, although its diagnostic sensitivity for internal endometriosis is limited (5). Most recently, endoluminal ultrasonography was introduced to evaluate ureteropelvic junction obstruction and help avoid crossing vessels during endoscopic treatment of this condition (12).

Therapeutic options are medical therapy, surgery or combination of them. The main goal of therapy is release of ureter stenosis to save normal function of kidney and should be tailored for each patient relative to the extent of disease and degree of stenosis. Medical therapy with the aim of hormonal therapy is indicated for early stage disease, and is not recommended for advanced disease due to the high incidence of recurrence.. Historically, the role of medical therapy has been in the management of residual disease (5).

Surgical therapy can be categorized into minimally invasive and conventional

open surgical treatment options. When the disease is more extensive, it includes total abdominal hysterectomy and bilateral salpingophorectomy with nephrectomy albeit if the kidney is functionless. In the presence of good renal function and less extensive pelvic involvement, only simple release of stenotic ureter is sufficient. Nowadays, minimally invasive procedures such as ureterostomy, laparoscopic ureterolysis and reimplantation can be performed with minimal morbidity (15;16). Finally, combination therapy may be used to minimize the endometriotic mass and help simplify the operation.

Here we described two cases of ureteral endometriosis, both of them with chief complaints of vague abdominal and pelvic pain in a period of at least one year before admission, unfortunately, by the time of diagnosis both of them had severe hydronephrosis.