

Urethral caruncle: a lesion related to IgG4-associated sclerosing disease?

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ABSTRACT

Aims Urethral caruncle is a benign, polypoid urethral mass that occurs almost exclusively in postmenopausal women. Despite that these lesions are routinely managed with topical medications or excision, their pathogenesis is not well understood. We investigated the possibilities of autoimmune, viral and inflammatory myofibroblastic proliferations as possible aetiologies.

Methods In 38 patients with urethral caruncle, we utilised immunohistochemistry for immunoglobulin G (IgG) and IgG4 to assess for a potential autoimmune aetiology. Immunohistochemistry was performed in nine patients for Epstein–Barr virus, BK virus, human herpesvirus 8, human papillomavirus, adenovirus and anaplastic lymphoma kinase.

Results Four patients (11%) showed infiltrates of ≥ 50 IgG4-positive plasma cells per high power field, of which all showed an IgG4 to IgG ratio greater than 40%. A statistically significant difference ($p < 0.01$) was detected in the mean number of IgG4-positive cells (14.73 per high power field) compared with control benign urethral specimens (mean, 1.19). One patient with increased counts below this threshold had rheumatoid arthritis; none had documented autoimmune pancreatitis or other known manifestations of systemic IgG4-related sclerosing disease. All lesions showed negative reactions for the viral and inflammatory myofibroblastic markers.

Conclusions Urethral caruncle is a benign inflammatory and fibrous polypoid urethral mass of unclear aetiology. It appears unrelated to viral infection and lacks the abnormal expression of anaplastic lymphoma kinase protein, as seen in inflammatory myofibroblastic tumours. Increased numbers of IgG4-positive plasma cells in a subset of lesions raise the possibility that some cases may be related to the autoimmune phenomena of IgG4-associated disease.

INTRODUCTION

Urethral caruncle is a benign polypoid urethral lesion, almost exclusively occurring in postmenopausal women,^{1–3} composed of hyperplastic urothelium or squamous epithelium overlying an inflamed, oedematous, vascular or fibrotic stroma.^{4–5} In contrast to urethral mucosal prolapse, which results in circumferential mucosal herniation, urethral caruncle forms a focal mass lesion. Symptoms include pain or bleeding, although many patients are asymptomatic.^{3–5–6} Urethral caruncle has been hypothesised to originate due to chronic irritation and mucosal herniation,³ perhaps as a result of atrophy and oestrogen deficiency. Despite these hypotheses, however, the pathogenesis has not been thoroughly investigated and

remains poorly understood. Occasionally squamous cell carcinomas or other neoplasms⁴ clinically mimic urethral caruncle and, rarely, carcinoma has been described to arise in a caruncle;^{7–9} however, they do not appear to have convincing premalignant potential.¹⁰ A small subset of caruncles occur in patients with concurrent or metachronous urothelial carcinoma; however, a conclusive link between these two diseases is not clear.⁵ Often, treatment is undertaken first conservatively with topical oestrogen, topical anti-inflammatory agents or sitz baths,³ and surgical excision is generally reserved for larger, refractory lesions, or those with an uncertain diagnosis.^{3–11} However, data regarding efficacy of such therapies are limited.^{3–5} In order to better understand the aetiology of these lesions and to guide future therapeutic strategies, we assessed patients with urethral caruncle for evidence of autoimmune, viral and inflammatory myofibroblastic origins.

MATERIALS AND METHODS

Tissue blocks from urethral caruncle biopsy or excision specimens were retrospectively retrieved from the surgical pathology files of the authors' institutions. Clinicopathological features for these cases were previously reported.⁵ Immunohistochemistry was performed on an automated immunostainer for 38 biopsy or excision specimens with antibodies directed against immunoglobulin G4 (IgG4). As previously recommended for diagnosis of IgG4-associated disease,^{11–12} the numbers of IgG4-positive plasma cells were counted in at least three high power fields in the areas of highest density. The mean of these three values was calculated and utilised for statistical evaluation. For lesions showing a mean of greater than or equal to 50 IgG4-positive plasma cells per high power field, IgG4 to IgG ratio was calculated by comparison with immunohistochemical-stained slides with antibody to IgG, quantitated in the same manner.^{12–13} A control set of benign urethral biopsy and excision specimens ($n=21$) was also retrieved from the pathology archives and studied comparatively in the same manner, selected from a consecutive series of urethral specimens that included a spectrum of acute and chronic inflammation. Pathological diagnoses for these control specimens included: benign squamous mucosa or squamous metaplasia (with variable acute and/or chronic inflammation; $n=9$), urethral diverticulum ($n=4$), benign urethral mucosa with chronic inflammation ($n=3$), squamous papilloma ($n=1$), polypoid urethritis ($n=1$), urethral polyp ($n=1$), features consistent with collapsed periurethral

duct cyst (n=1), and ulcer with granulation tissue (n=1). Both urethral caruncle and control specimens were included in the study if tissue blocks were available and contained sufficient material for assessment of the subepithelial inflammatory cell infiltrate. The mean number of IgG4-positive plasma cells in the urethral caruncle specimens was compared with the control group using a two-tailed student t test. A p value of <0.05 was considered to be statistically significant.

A subset of urethral caruncle specimens with sufficient tissue material (n=9) was also studied with antibodies directed against Epstein–Barr virus (EBV) latent membrane protein-1 (LMP1), adenovirus, human herpesvirus 8 (HHV8), human papillomavirus (HPV), BK virus and anaplastic lymphoma kinase-1 (ALK1).

IgG4 stain was performed with monoclonal mouse antihuman IgG4 antibody (clone HP6025, 1:2000 dilution; Zymed, Carlsbad, California, USA). Immunohistochemical stains for IgG were performed with polyclonal rabbit antihuman IgG antibody (ready to use; Zymed). Immunohistochemical stains for EBV were performed with monoclonal mouse anti-EBV LMP1 antibody (clone CS.1-4, 1:400 dilution; DAKO Corp, Carpinteria, California, USA). Adenovirus stain was performed with monoclonal mouse antiadenovirus antibody (clone M58 +M73, dilution 1:50; LabVision, Fremont, California, USA). HHV8 stain was performed with rat monoclonal anti-HHV8/Kaposi sarcoma-associated herpesvirus antibody (LN 53, 1:50 dilution; Advanced Biotech, Columbia, Maryland, USA). Staining for HPV was performed with a monoclonal mouse antihuman HPV antibody (clone K1H8, 1:25 dilution; DAKO Corp). BK virus stain was performed with a monoclonal mouse anti-SV40 polyoma virus antibody (clone MRQ4, 1:50 dilution; Cell Marque, Rocklin, California, USA). ALK immunostaining was performed with a monoclonal mouse antihuman CD246, ALK protein antibody (clone ALK1, prediluted; DAKO Corp).

RESULTS

Immunohistochemical staining with antibodies directed against IgG4 revealed an overall mean IgG4-positive plasma cell count in the 38 urethral caruncle specimens of 14.73 (SD, 32.98; range 0–185.67), compared with the control cases of other benign urethral biopsy or excision specimens which had a mean of 1.19 IgG4-positive plasma cells per high power field (SD, 2.12; range 0–8.67). A statistically significant difference was detected for the overall mean IgG4-positive plasma cell count ($p<0.01$) between the two groups. Counts of greater than 50 IgG4-positive plasma per high power field were detected in four patients, all of whom also had an IgG4 to IgG ratio of 40% or greater.^{12 13} Eight additional patients had counts of greater than 10 positive cells per high power field, while the remaining patients had less than 10 positive cells per high power field. Of the 21 control cases of other benign urethral biopsy or excision specimens, none showed numbers of IgG4-positive cells meeting the study thresholds.^{12 13}

Histologically, the urethral caruncles with increased numbers of IgG4-positive plasma cells meeting the study cut-offs (greater than or equal to 50 cells per high power field and IgG4 to IgG ratio of 40% or greater) showed variable degrees of stromal fibrosis and chronic inflammatory cell infiltrates, predominantly composed of lymphocytes and plasma cells (figure 1). One lesion showed large, dilated blood vessels with organising thrombosis and associated infiltrates of numerous plasma cells, although fibroblastic obliteration of the vascular lumina was not

identified. In a single patient with documented history of rheumatoid arthritis, mean IgG4-positive plasma cell count was 40 cells per high power field, with an increased ratio of 73% IgG4 compared with total IgG-positive cells. Serum measurements of overall IgG or subclass IgG4 were not available in the medical records for any of the patients meeting these thresholds; none had a documented history of autoimmune IgG4-related sclerosing disease involving other organ systems.

Of the nine cases studied for the presence of viral markers, none showed positive staining for EBV LMP1, adenovirus, HHV8, HPV or BK virus. Positive reactions for ALK1 in the stromal cells were not identified in any of the nine lesions studied.

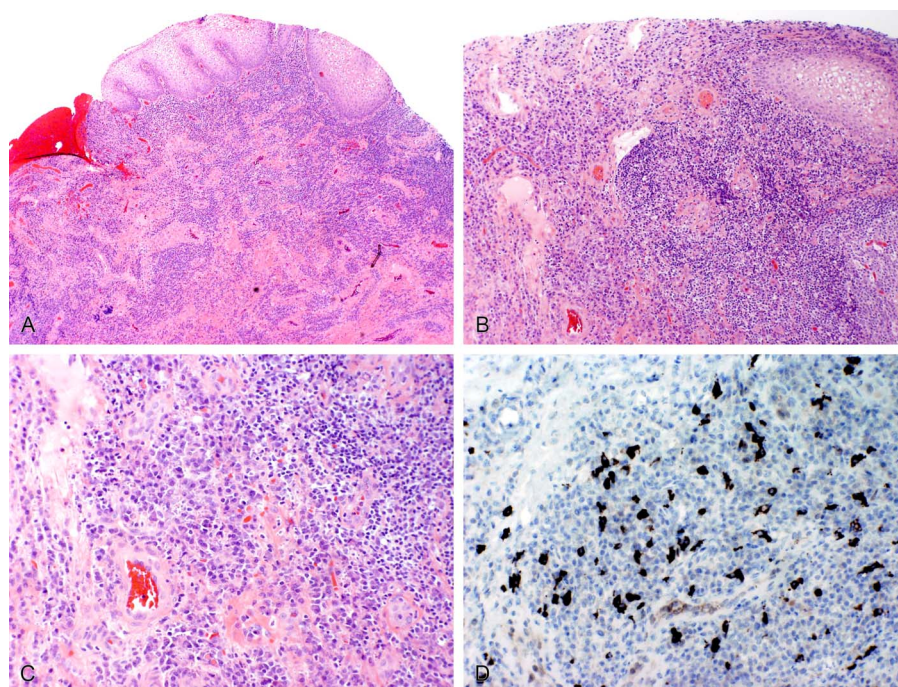
As previously reported,⁵ additional clinical follow-up information included recurrence of the caruncle in two of these 38 patients, one of whom had increased IgG4-positive cells and an increased IgG4 to IgG ratio, and one of whom was the single patient with rheumatoid arthritis and increased IgG4-positive cells below the study cut-off of 50 cells per high power field. No patient developed carcinoma of the urethra, although a subset of patients (four in this study) had urothelial carcinoma with variable temporal relationships to the treatment of their urethral caruncles.⁵

DISCUSSION

Urethral caruncle is a benign polypoid urethral mucosal lesion that occurs almost exclusively in postmenopausal female subjects, with incompletely understood pathogenesis.^{1 3–6 10 11} In order to better understand the mechanism of development of these lesions and to potentially improve therapeutic strategies, we applied immunohistochemistry for a variety of markers of viral, autoimmune and other aetiologies, which have not been previously studied in urethral caruncle.

Recently, numerous inflammatory and sclerosing processes involving almost every organ system have been recognised as part of the spectrum of IgG4-associated diseases.^{12 13} Although autoimmune pancreatitis is the prototypical member of this group,^{14–16} a number of other disease processes have also been identified as potential manifestations of IgG4-associated sclerosing disease, affecting a variety of organ systems.^{12 13 17–28} Of note, the IgG4 subclass is the least common subclass of IgG,¹² with low antigen affinity and lack of activation of the classical complement pathway,²⁹ but it is over-represented in the sclerosing and inflammatory lesions of these disease processes. Raising the possibility that some cases of urethral caruncle may be related to IgG4-associated disease, a subset of our patients (n=4, 11%) had a marked increase in the number of plasma cells showing a positive reaction for IgG4 (with mean ≥ 50 per high power field) and an increased IgG4 to IgG ratio of >40%,^{12 13} in contrast to most patients with urethral caruncle, who had few or no significant numbers of IgG4-positive cells (0 or <10 per high power field). Similarly, 21 control cases of benign urethral diseases with a spectrum of acute and chronic inflammation showed very rare IgG4-positive plasma cells, none of which met these diagnostic criteria for IgG4-related sclerosing disease.^{12 13} Histopathological features in the four patients that met these thresholds included variable degrees of stromal fibrosis and chronic inflammation,⁵ in line with the morphological findings in patients with IgG4-associated diseases. Of these patients, one showed organising thrombosis of blood vessels, surrounded by infiltrates of plasma cells, although the fibroblastic proliferation obliterating the vascular lumina (obliterative phlebitis) that is seen in some cases of

Figure 1 Urethral caruncle (panels A–D from the same specimen). (A) Hyperplastic squamous epithelium overlying a fibrovascular stroma containing small, prominent blood vessels and a dense, diffusely arranged inflammatory infiltrate. (B) Small stromal blood vessels surrounded by dense inflammatory infiltrate. (C) High magnification, showing primarily lymphocytes and plasma cells. (D) Immunohistochemical staining for immunoglobulin G4 (IgG4), showing increased numbers of IgG4-positive cells.



autoimmune pancreatitis was not evident. Notably, this finding is not uniformly demonstrable in all organ systems involved by the disease and is only present in some subtypes of autoimmune pancreatitis.^{12 15 30} None of these patients were known clinically to have manifestations of IgG4 sclerosing disease affecting other organs and serological levels of overall immunoglobulin and IgG4 were not available in these patients to lend additional support to this diagnosis. Although a serological increase in IgG4 is sometimes also a manifestation of these disease processes, it is not identifiable in all patients with established IgG4-associated sclerosing disease. Serum levels of IgG4 are most prominently elevated in patients with multisystem involvement.¹² Other features of IgG4-associated disease include a predilection for male patients, especially autoimmune pancreatitis.^{12 13} Urethral caruncle, in contrast, is seen almost exclusively in women. Nonetheless, some IgG4-associated diseases have been found to maintain the strong female predilection for diseases that affect particular body sites.^{30–36} One patient in this study had a history of rheumatoid arthritis and increased numbers of IgG4 plasma cells below the positive cut-off. Rheumatoid arthritis in particular has been noted to be associated with increased numbers of IgG4-positive plasma cells,^{21 37} despite that other features of the disease do not warrant its consideration as a member of the IgG4-associated disease family.¹² Several other conditions are considered to be unrelated to IgG4-associated disease, yet increased numbers of IgG4-positive cells can be found in biopsy or excision specimens.¹² Our findings raise the possibility that, in the appropriate clinicopathological context, some cases of urethral caruncle may be related to IgG4-associated autoimmune disease. The majority of urethral caruncles, however, does not appear to contain increased numbers of IgG4-positive cells and may be attributable to another, yet unclear aetiology.

We also investigated the possibility that an infectious process may contribute to the chronic inflammatory response present in urethral caruncle.³⁸ Viral processes, such as EBV, HPV, HHV8 and others, are well known to be involved in the

pathogenesis of proliferative epithelial or stromal lesions of various body sites. Other viral agents sometimes result in characteristic mucosal changes in the genitourinary tract or other body sites, such as adenovirus and BK virus. In our series, we were unable to identify evidence of such viral infections by immunohistochemistry, suggesting that these agents do not play a significant role in pathogenesis of urethral caruncle. Gene rearrangement for ALK and positive staining for ALK protein by immunohistochemistry are characteristic features in at least a subset of inflammatory myofibroblastic tumours,^{27 39} some of which affect the genitourinary tract.³⁹ Likewise, occasional examples of urethral caruncle have been reported that show atypical stromal cells, raising concern for a neoplastic stromal proliferation.⁴⁰ In this study, however, we found immunohistochemical staining for ALK protein to be uniformly negative, supporting a distinction between inflammatory myofibroblastic tumours of the genitourinary tract and urethral caruncle.

In summary, we utilised immunohistochemical analysis of protein expression to evaluate a number of possible aetiologies for urethral caruncle, an unusual polypoid lesion that occurs almost exclusively in postmenopausal women. A subset of lesions (11%) demonstrated markedly increased numbers of IgG4-positive plasma cells within the stroma and increased ratios of IgG4 to overall IgG-positive cells, raising the possibility that some cases may be related to IgG4-associated inflammatory and sclerosing disease. In contrast, the majority of lesions exhibited very low numbers of IgG4-positive cells (<10 per high power field). We did not identify immunohistochemical evidence of viral infection, suggesting that these lesions are unrelated to infection with the multiple viral agents that result in mass-forming lesions or other mucosal abnormalities. Abnormal expression of ALK protein was not detected, in contradistinction to inflammatory myofibroblastic tumours, which sometimes also affect the genitourinary tract and may be a differential diagnostic consideration, especially when atypical stromal cells are present.

Take-home messages

- Immunohistochemical analysis of protein expression to evaluate a number of possible aetiologies for urethral caruncle, an unusual polypoid lesion that occurs almost exclusively in postmenopausal women, showed a subset of lesions (11%) demonstrating markedly increased numbers of IgG4-positive plasma cells within the stroma and increased ratios of IgG4 to overall IgG-positive cells.
- Immunohistochemical evidence of viral infection was not identified, suggesting that urethral caruncles are unrelated to infection with the multiple viral agents that result in mass-forming lesions or other mucosal abnormalities.
- Abnormal expression of anaplastic lymphoma kinase protein was not detected, in contradistinction to inflammatory myofibroblastic tumours, which sometimes also affect the genitourinary tract and may be a differential diagnostic consideration, especially when atypical stromal cells are present.

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