Granulomatous prostatitis

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INTRODUCTION

Granulomatous prostatitis (GnP) accounts for 0.8–1% of benign inflammatory conditions of the prostate [1–3]; it mimics prostate cancer clinically, histologically, biochemically, ultrasonographically and radiologically [4,5]. Carcinoma was clinically suspected in up to 59% of cases of GnP [3] and the rate of histological similarity with carcinoma in one series was 20% [3]. Carcinoma also coexists in 10–14% of patients with clinically diagnosed GnP [2,6]. In addition, GnP shares some cytological features with other conditions of the prostate, which can lead to an erroneous diagnosis [2]. In 1987 Stillwell *et al.* [3] published the largest series of tissue-diagnosed GnP and addressed hitherto unanswered questions about the condition. This was before the wide clinical use of PSA assays and TRUS-guided prostate biopsies for detecting prostate cancer.

In England, patients referred with suspected prostate cancer are tracked through the health system to monitor the achievement of time-targets for diagnosis and treatment. The management of patients with biopsy-confirmed prostate cancer is discussed at the multidisciplinary team meetings. A decision on the subsequent management of those patients with negative biopsies is based on several clinical features, but also on the pathological finding on the needle biopsy. One such uncommon finding is GnP. We present a brief but timely review on this heterogeneous entity, and discuss the dilemma of clinical management, especially when GnP is found on prostatic biopsies.

CLASSIFICATION

The classification of GnP is controversial. After a 32-year review of the cases at the Johns Hopkins Hospital, Epstein and Hutchins [7] classified GnP into specific, nonspecific, after TURP, and allergic granulomatous prostatitis. Miralles *et al.* [8], in 1990, proposed a pathogenetic classification into non-infectious GnP (allergic or non-allergic origin) or specific/infectious GnP (due to tubercular or other organisms). Stillwell *et al.* [3] proposed expanding the allergic class and termed it 'GnP secondary to systemic granulomatous disease'. However, it is the system proposed by Epstein and Hutchins [7] that is now widely accepted and generally used.

CAUSES

In most cases the cause of GnP is unknown [1], but GnP can occur after various predisposing/precipitating events, e.g. UTI (71%) [3], TURP/open prostatectomy [4], needle biopsy and instillation of BCG into the bladder [9]. Non-specific GnP (NSGnP) is usually an incidental finding, with an incidence of <3.4% in unselected series of patients [10]; it is detected in 0.44% of routine prostatectomy specimens [4] and in 0.29 [4] to 3.3% [8] of needle prostate biopsies. GnP generally occurs in 1.3% of patients after intravesical BCG treatment [11].

Some authorities consider that the cause of NSGnP is autoimmune-based [12], with a HLA-DR15-linked T-cell response against proteins in prostatic secretions, principally PSA [1]. The aetiological significance of NSGnP has also been attributed to acute non-specific prostatitis, with local hypersensitivity and/or simple foreign-body reactions considered to be pathogenetic factors.

Specific GnP (SGnP) is caused by identifiable infectious agents, most commonly *Mycobacterium tuberculosis*, and is referred to as tuberculous prostatitis (TP). Other rare causative agents of SGnP are fungi, syphilis, brucellosis, viruses and parasites [2]. *Escherichia coli* has also been implicated [13,14].

GnP can occur after TURP and is probably due to a reaction to altered epithelium and stroma [7]. It resembles rheumatoid nodules histologically and can have palisading histiocytes [7,15].

The identification of frequent eosinophils might suggest the diagnosis of allergic GnP. In addition to eosinophils, this exceedingly uncommon type of GnP is usually associated with a history of a systemic allergic condition such as asthma and vasculitis [15], i.e. Wegener's granulomatosis [16] or Churg–Strauss syndrome [3]. Both NSGnP and GnP after TURP, which might be indistinguishable histologically [13], can be associated with eosinophilic infiltration as a result of local hypersensitivity or as part of the early inflammatory response [7,12].

PATHOLOGY AND DIAGNOSIS

The pathogenesis of GnP remains unknown but extravasation of prostatic secretions due to inflammation (from infection, surgical diathermy or tissue necrosis), and blockage and rupture of prostatic ducts appear to be important factors in the development of granulomas. These processes can occur in normal, carcinomatous or most commonly in a nodular hyperplastic prostate gland [17]. The distribution is generally periglandular with some glandular destruction [1].

GnP is a histopathological diagnosis characterized by a pattern of focal (20%, [3]) or extensive chronic inflammatory lesions consisting of a large nodular infiltrate of epitheloid histiocytes, multinucleated giant cells, lymphocytes, and plasma cells centred in the prostatic lobules, with or with no tissue necrosis. The hallmark criterion for a diagnosis of GnP is the presence of distinct epitheloid granulomas [2]. Histological samples that do not meet this criterion are classified as chronic prostatitis or

TABLE 1 Differentiation of GnP from chronic prostatitis

Method	GnP	Chronic prostatitis
Clinically	Firm to hard painless prostate	Boggy or firm prostate with variable tenderness
Cytologically		
Epitheloid granulomas	+	–
Epitheloid histiocytes	+	–
Tissue necrosis	+/–	–
Eosinophils	+	–
Cellularity (density of inflammatory cells – macrophages, lymphocytes and plasma cells)	Usually minimal	Usually high
Multinucleated giant cells	Usually foreign body or Langhan's type	Usually Touton's type

chronic recurrent prostatitis if there are chronic inflammatory cells, according to Leistenschneider and Nagel's criteria [18]. The cytological differences between chronic prostatitis and GnP are shown in Table 1.

The diagnosis of GnP is made by needle biopsy or at TURP in 94% of cases [3] and NSGnP is the most commonly diagnosed entity [5,7], accounting for up to 62.5% of all GnP in some series [2], while the post-TURP type is the second most common. Together, NSGnP and post-TURP type constitute 95% of cases of diagnosed GnP [3].

NSGnP can be diagnosed in fine-needle aspirates of the prostate when granulomas and other inflammatory cells are present, and TP when there is also caseation. Other forms of GnP require more clinical data and ancillary techniques [2,8].

The diagnosis of TP is based on finding a caseating lesion or using special stains (auramine rhodamine) on the biopsy specimen, but there is a greater chance of sampling a non-caseating granuloma than a caseating lesion by needle biopsy when both are present, and special stains might be negative for tuberculosis because of the smallness of the tissue sample. Therefore, the absence of caseation on biopsy does not necessarily exclude tuberculosis, and if the clinical suspicion of TP is high, and if non-caseating lesions are found on needle biopsy, a second biopsy specimen should be taken for culture only [19]. Miralles *et al.* [8] proposed that when inflammation is slight, phagocytosis is absent, and caseous necrosis is present, TP should be suspected. NSGnP can mimic TP when the granulomatous inflammation is associated with liberated prostatic secretions and debris.

It is also important to distinguish the various types of GnP from prostate cancer, and a panel of immunohistochemical tests can reliably distinguish between these conditions. This includes Diff-Quik™ stain (Dade Behring, Inc., Deerfield, IL, USA) for epithelial atypical cells [8], antibodies to high molecular weight cytokeratin (34βE12), α-methylacyl-CoA racemase, PSA, prostatic acid phosphatase, CD68 and leukocyte common antigen [5].

CLINICAL AND BIOCHEMICAL FEATURES

Most cases of NSGnP occur in patients aged >50 years [3,17]; the median (range) age of patients with NSGnP is 62 (18–86) years [3], with a mean of 54–65 years [10,17].

This disease entity is poorly defined clinically and features may include LUTS, especially frequency and dysuria, acute urinary retention, pyuria and haematuria. A fifth of cases present with a triad of sudden-onset high fever, symptoms of prostatitis and a diffuse or nodular painless firm to hard enlargement of the prostate, with an increased consistency on DRE [4]; the last makes clinical differentiation from cancer difficult [8]. However, chronic prostatitis can present with a 'boggy' or firm prostate with variable tenderness (Table 1). GnP can also cause a significant but transient increase in serum PSA level [20].

NATURAL HISTORY AND TREATMENT

Although the inflammatory process in GnP can be fulminant, the natural history is that of slow but complete resolution, and therefore patients should be reassured. As most GnP is of the non-specific type, therapy is mainly supportive, with local therapy including hot sitz baths, fluids and temporary catheterization; up to 62% of patients have spontaneous resolution [3]. Antibiotics (empirical or based on urine culture sensitivity) should be given for documented UTI. About 10% of cases can be refractory to conservative management and will eventually need a prostatectomy [3].

The management of SGnP depends on the causative factor and appropriate medical therapy should be instituted. Any associated or underlying systemic disease should be identified and treated, and this often makes for a dismal prognosis in the allergic type. However, recurrences are rare, although the prostate might remain abnormal on DRE for years.

DISCUSSION

The diagnosis of GnP is based on a histological finding of epitheloid granulomas with or with no other chronic inflammatory cells. This is important, as BPH, chronic prostatitis and prostatic infarctions can resemble GnP cytologically. Despite its low incidence, GnP is currently diagnosed more frequently due to the increase in TURP and prostatic biopsy procedures, and the widespread use of intravesical BCG therapy for high-risk superficial bladder cancer. NSGnP and the post-TURP type are the most common granulomatous lesions of the prostate, while the allergic type is uncommon. As to the clinical manifestation and treatment, GnP is not a specific entity, but has characteristic histopathology. The major concern is the possibility of GnP being mistaken for prostate cancer on several fronts, but especially clinically in more than half of cases. This is complicated in that both conditions can coexist. There is no pattern on TRUS or MRI that allows a specific diagnosis of GnP or differentiation from prostate adenocarcinoma. Several investigators have stressed that GnP can be erroneously diagnosed as carcinoma, but we think that if the pathologist is aware, this mistake is unlikely to occur, especially with the use of special staining techniques to clarify any doubts.

It is important to recognize the association of GnP, especially NSGnP, and adenocarcinoma

of the prostate, and therefore emphasize the necessity of wide sampling of prostatic surgical specimens with GnP to exclude a concurrent prostatic adenocarcinoma, because of the association between these two entities. The association of the two conditions is not surprising, as prostatic adenocarcinoma is prevalent in middle-aged and elderly men. A panel of immunohistochemical tests can reliably distinguish between these conditions. It is important to make this distinction, as the prognosis of NSGnP is excellent, with most cases resolving spontaneously, although some will require local therapy, symptomatic or specific therapy.

If GnP is diagnosed on needle biopsy after referral for a high PSA level and an abnormal prostate on DRE, reports suggest the treatment of GnP as indicated. This should resolve over a period of months, and the PSA level should return to the normal range for the patient. However, if this does not occur and the prostate still feels abnormal, then a re-biopsy is warranted. For tracking within the health system, the 'clock' can be stopped during this period, if there remains a strong suspicion, or the patient can be taken off tracking, provided a clear follow-up plan is put in place.

CONFLICT OF INTEREST

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