Tumours of the male genital tract

Marie O'Donnell

Abstract

This article discusses pathological features of tumours of the male genital tract. Carcinoma of the prostate is common and represents an increasing burden to the NHS in terms of management and treatment. We focus on recent changes to grading and discuss issues around pathological diagnosis. Tumours of the testes represent the greatest success story of cancer treatment over the past several decades. We review the pathological features of the commonest tumours focussing on prognostic features. Carcinoma of the penis is rare but appears to be increasing in incidence. It requires more awareness amongst the public and general practitioners to prevent presentation at an advanced stage. We focus on pre-invasive lesions and on the pathological staging of this disease.

Keywords Pathology; penile carcinoma; prostate carcinoma; testicular tumours

Tumours of the prostate gland

Background, epidemiology and risk factors

Prostate cancer is the most common cancer in men in the United Kingdom. It accounts for 25% of all male cancer diagnoses. One in eight men will receive the diagnosis sometime during their life parallelling breast cancer rates in women. In 2012, there were 43,436 new cancer cases in the UK with 10,837 deaths ascribed to prostate cancer. Currently, it is estimated that men have an 84% 10-year survival from the disease. While rates have started to decrease in those patients >75 years, it continues to rise in individuals between 45 and 74 years. The increasing incidence probably reflects a combination of a true increase in the number of cases as well as the incidental detection of carcinoma because of routine blood tests for serum PSA.

The exact cause of prostate cancer is not fully understood and is probably multifactorial. There is an association with strong family history, race, increased androgen levels, diet and probably other environmental factors. There is an increased risk in those men who have one or more first degree relatives with prostate cancer especially if the relative had a diagnosis before the age of 60. Those men who are of Afro-Caribbean extraction have a greater risk of developing prostate cancer compared with Caucasian men, but Asian men appear to have a lower incidence of the disease. In recent years, there has been an increasing recognition that men with mutation of the BRCA2 gene have almost a twentyfold increase in prostate cancer risk. Many of these patients develop their carcinomas at an earlier age and appear to have an aggressive form of the disease. In some studies, familial prostate cancer patients were found to have alterations to chromosome 1,17 and the X chromosome. It is possible that with increasing knowledge, selective screening and monitoring of high risk groups may be able to be initiated.

Marie O'Donnell *MB BCh BAO (NUI) FRCPath is a Consultant in Urological Pathology at the Western General Hospital, Edinburgh, UK. Conflicts of interest: none declared.*

Diagnosis

While some patients may present with symptoms related to bladder outlet obstruction or to metastatic disease, the majority of patients with prostatic carcinomas are diagnosed following the identification of an elevated serum PSA and the subsequent performance of ultrasound guided transrectal prostatic core biopsies. Practices vary between individual units but in most cases 10–12 prostatic core biopsies are taken from prescribed areas of the peripheral zone of the prostate and also from the apex. Over the past decade, Pathology Departments in the UK have seen a massive increase in the number of prostate core biopsies performed. At least 50% of those biopsied will show evidence of adenocarcinoma. If the biopsies are benign but there remains a strong clinical suspicion or the PSA remains elevated/continues to rise, the current practice in many centres is to perform a multiparametric MRI scan to try and identify any discrete abnormality that can be targeted on repeat biopsies. Transperineal biopsies can permit sampling of areas of the prostate that are not readily accessible by transrectal biopsies. It produces a greater number of biopsies to be reviewed and is said to be less painful compared with the transrectal approach. This method can target anterior located tumours which are often associated with negative TRUS prostatic biopsies. It is predicted, that with increasing use of multi-parametric MRI scans, that in the future, patients may have an initial assessment with MRI and only those with a distinct abnormality will be subjected to targeted biopsies. Prostatic carcinoma can also be identified on TURP specimens. Prior to the advent of PSA testing and TRUS biopsies, it was estimated that between 15% and 20% of prostate chips contained adenocarcinoma. In some cases, this was low volume well differentiated transition zone cancer and was probably incidental. In other cases, it was poorly differentiated, reflecting extension of a bulky peripheral zone carcinoma into the transition area of the prostate.

The histological diagnosis of prostate adenocarcinoma is primarily based on the abnormal architectural growth pattern of the neoplastic glands and relies less on cytological atypia. In lower grade carcinomas, the glands are typically well formed and distinct, they may contain small amounts of blue tinged mucin or crystalloid material. Unlike benign glands, they are composed of a single layer of cuboidal to low columnar epithelium without the second surrounding basal cell layer. This feature can be exploited in difficult cases where there is minimal carcinoma present. The application of immunohistochemistry against basal cell antigens can demonstrate in many cases the difference between benign glands and malignant glands. Use of racemase immunohistochemistry can also be of use as it is more likely to show stronger expression in malignant foci. Many units use combinations of both racemase and basal cell markers to investigate difficult cases. These stains are particularly helpful in benign mimickers of well differentiated carcinoma such as atrophy, adenosis, inflammatory/reactive atypia and small fragments of seminal vesicles (Figure 1). As prostatic adenocarcinomas become less well differentiated, they show increased complexity of the architectural growth pattern with diminished gland formation

and more obvious nuclear enlargement and pleomorphism. A particularly notable feature of prostate cancers is the presence of prominent nucleoli. While acinar adenocarcinoma accounts for the majority of adenocarcinomas of prostate, less common variants are also recognized in probably 5% of cases. These include ductal adenocarcinoma of prostate which can present as a papillary lesion within the prostatic urethra and which is associated with a more aggressive course and neuroendocrine/small cell carcinoma which mimic identical tumours found elsewhere in the body and which is often treated with neoadjuvant chemotherapy.

Grading

The Gleason Grading System is the most frequently used system worldwide. It divides prostatic adenocarcinoma into five distinct grades based on overall glandular differentiation and pattern. There have been modifications of the Gleason Grading System since the original publication. The most recent of these was in 2005 when a modified Gleason Grading System was published. Gleason recognized that many tumours show mixed patterns and that the overall prognosis is better reflected by using a combination of the grades present (Figure 2). He identified the dominant pattern (primary) with the second most frequent pattern present (secondary) to give an overall Gleason score. If a carcinoma is found to be composed of a single grade then the overall grade is doubled to give the final score. In addition, it is now recognized that in a portion of cases, a third or tertiary Gleason grade is present and that this should be reported if it is of higher grade than the primary or secondary elements e.g. $3 + 4 + 5$ should be regarded as $3 + 5 = 8$. Over recent years, some deficiencies of Gleason grading have been recognized. Gleason grades 1 and 2 are not identifiable in prostatic core biopsies and Gleason pattern 2 is infrequently recognized in prostatectomy and TURP specimens. By default, the lowest score generally recorded is $3 + 3 = 6$. This can become problematic when discussing pathological findings with patients as a score of 6 out of a total of 10 is regarded as being a good prognostic carcinoma. Therefore, in recent years, a move to produce a five tier prognostic grade grouping has been recommended and has recently been adopted by UK uropathologists with both Gleason score and prognostic grade group being included in pathology reports. Group 1 which is the most favourable group represents a Gleason score of 6 or less while Group 5, the least favourable, represents a Gleason score of 9–10. These groups are very strongly associated with prognostic outcome and it is most likely that this will replace the Gleason Grading System going forward (Table 1).

Prostatic intraepithelial neoplasia (PIN) and intraductal carcinoma

Prostatic intraepithelial neoplasia is an atypical intraduct epithelial proliferation composed of atypical cells with prominent nucleoli. These ducts retain a basal epithelial layer which can be demonstrated on immunohistochemistry. While lower grades of PIN exist, inter and intra observer variability means that only high grade PIN is commented upon in prostatic core biopsies. It is estimated that high grade PIN in isolation will be seen in up to 10% of prostatic core biopsies. Invasive carcinoma can be found in up to 25% of patients with high grade PIN on follow up. Patients with multifocal bilateral high grade PIN have a higher risk of adenocarcinoma being found on repeat biopsy.

High grade PIN is not to be confused with intraductal carcinoma (IDC) which represents spread of malignant cells along the large ducts of the prostate. This is almost always seen in association with invasive adenocarcinoma usually of high grade. It is recognized as an independent adverse prognostic factor with many cases having extraprostatic spread at the time of diagnosis.

ASAP – atypical small acinar proliferation

Atypical small acinar proliferation is not a diagnostic entity but reflects an atypical focus seen by the pathologist on biopsy. Despite the examination of multiple levels and the performance of immunohistochemistry, the focus is too small to be confident about a definite diagnosis of adenocarcinoma. It is estimated, that an isolated diagnosis of ASAP is seen in between 1% and 5% of prostatic core biopsies. Careful follow up of this group of patients is warranted as various studies have demonstrated that in 34–60% of cases, adenocarcinoma of the prostate will be identified on subsequent biopsies. It may be worth considering MRI in these patients to target any areas of abnormality. Occasionally the term PINATYP will be used to indicate that the focus of atypical glands is seen in close association with a focus of high grade PIN and may represent an outpouching of the duct affected by dysplasia but in which a tiny focus of invasive carcinoma cannot be fully excluded.

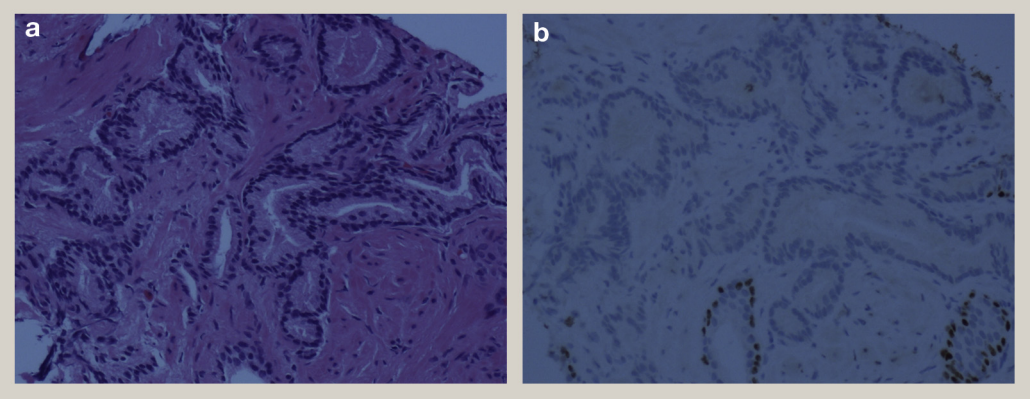

Figure 1 (**a**) H&E & (**b**) P63 immunohistochemistry. A tiny proliferation of atypical glands found in a single core of a TRUS biopsy. The neoplastic nature of the malignant glands is highlighted by the absence of basal cells surrounding the glands using immunohistochemistry to P63.