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ORIGINAL ARTICLE

The significance of atypical urine cytology in the face of normal investigations—Is extended investigation and follow-up required?

E.H. Streeter[a,*], G.D.H. Turner[b], R. McCormick[c], I.S. Roberts[b], J. Crew[c]

[a] *Department of Urology, Kent and Canterbury Hospital, Ethelbert Road, Canterbury, Kent CT1 3NG, United Kingdom*
[b] *Department of Cellular Pathology, John Radcliffe Hospital, Oxford, United Kingdom*
[c] *Department of Urology, Churchill Hospital, Oxford, United Kingdom*

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Urine cytology;
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Summary
Objective: To examine the natural history of patients identified with atypical urine cytology in the face of normal investigations, and thus provide guidance on the need for extended follow-up and investigation of such patients.
Patients and methods: All patients identified over a 2-year period to have atypical urine cytology on Cytospin analysis and Papanicolaou staining were audited over a 5-year follow-up period. Clinical records, histopathology and radiology databases were independently searched. Patients were intensively investigated with cystoscopy and a range of upper tract imaging.
Results: 126 patients were identified to have atypical urine cytology, and 77 of these had no urothelial tumour found. In these normal patients, only 12/48 who had further samples taken showed persistent atypia. 11/77 normal patients had another urological pathology which may have explained their atypical urine cytology. No patient presenting for the first time later went on to develop urothelial malignancy in the face of negative initial investigations.
Conclusion: In the group of patients in which cystoscopy and urography show no urothelial malignancy, the finding of atypical urinary cytology does not predict the development of later urothelial tumour, and does not require prolonged follow-up, repeat cytological testing or further imaging.

* Corresponding author. Tel.: +44 1227 766877.
E-mail address: edwardstreeter@doctors.org.uk (E.H. Streeter).

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Introduction

Urine cytology is frequently used in the assessment of patients with suspected urothelial carcinoma. AUA best practice guidelines recommend its use in all high risk patients, and in low risk patients where its use may defer the requirement for cystoscopy [1]. However, cytological examination often leads to a diagnosis of atypia, without definitive evidence of malignancy. Atypia varies in degree from mild to severe. The former may result from non-neoplastic processes such as inflammation, calculi, viral infection, catheterisation or reactive non-neoplastic proliferations of the urothelial tract. The specificity of atypia as a sign of malignancy is therefore lower with milder forms of cytological change. A strongly abnormal result is highly predictive for transitional cell cancer or carcinoma in situ (90% positive predictive value), however only as few as 30% of low grade tumours will produce a positive result.

Some studies have attempted to identify cytological criteria which could distinguish between these causes of atypia [2]. The use of biomarkers for malignancy seems a promising adjunct to urine cytology, but although most are more specific they are often less sensitive than routine cytological examination at diagnosing low grade lesions [3]. Presenting complaints such as haematuria or lower urinary tract symptoms in the absence of haematuria (LUTS) have not been demonstrated to give additional guidance, nor has the presence of the cytological finding of inflammatory cells or the number of atypical cells in the specimen. In an attempt to increase sensitivity and specificity of urine cytology other ancillary tests have been suggested, such as fluorescence in situ hybridisation [4] or urinalysis of protein biomarkers such as matrix metallo-proteinases or telomerase (reviewed in [5]). However routine cytological examination remains the gold standard for diagnosing the presence of atypical or frankly malignant cells exfoliated from the bladder within the urine.

The sensitivity and specificity of any screening test depends on the accurate ascertainment of subsequent rates of disease on follow up. The frequency with which urine cytology is performed as an investigative test has increased, partly fuelled by algorithm based diagnosis and an increase in rapid access haematuria clinics. Such patients are subject to increasing levels of investigation, such as flexible cystoscopy and CT urography, due to the difficulty of excluding upper tract disease.

One study which attempted to correlate the finding of atypia with subsequent malignant diagnosis was flawed by a limited cystoscopy rate of only 59% [6]. Uncertainty thus remains as to what extent these patients require investigation, and whether atypia (as a single or persistent finding) signifies a current or future risk of developing urothelial carcinoma. No study has looked at the clinical significance of a finding of cytological atypia in a population of newly presenting patients who prove normal on subsequent investigation. The aim of this study was to provide further information on the natural history of the patient found to have atypical urine cytology, to determine if extended investigation and follow-up are warranted.

Methods

All patients diagnosed with atypical urine cytology seen in our department between 1st January 2000 and 31st December 2001 were audited. Patient records were searched individually for diagnoses and clinical details, whilst pathology and radiology databases were searched independently for missed data. Data to the end of 2006 were included, thus giving a minimum follow up period of 5 years. Following initial investigation, routine repeat imaging was not performed, but further investigation initiated dependent on symptom changes.

Urine cytology was performed by four consultant cytopathologists. The method of urine collection was usually a mid-stream void, though occasional samples from ureteric aspiration are included. Samples were processed using standard Cytospin preparation and Papanicolaou staining.

Statistical analysis was performed using Microsoft Excel, employing chi-square and 2-tail *t*-test with samples of unequal variance, as indicated.

Results

One hundred and twenty-six patients were identified. The mode of presentation of these patients is shown in Table 1. Of these, 113 (90%) underwent cystoscopy, whilst one patient had bladder cancer identified on imaging and was too unfit for further investigation, and one further patient had previously undergone a cystectomy. All but one patient underwent upper tract imaging as demonstrated in Table 2, with a tendency towards more intensive investigation in cases of macro or microscopic haematuria.

Forty-three urothelial tumours were identified, of which 42 were transitional cell and one squamous cell carcinoma. Thirty-five were located in the