CASE REPORT
Case Report: Large nested variant urothelial carcinoma –invasive malignancy masquerading as low grade disease [version 1; referees: 3 approved]
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Abstract
Introduction
The large nested variant of urothelial carcinoma (LNVUC) is a newly described and rare subtype of urothelial carcinoma. It is characterised by bland cytological features and a large nested architecture similar in appearance to low grade urothelial carcinoma with an inverted growth pattern. To date only 23 cases in a single series have been described.

Case Report
We describe the case of a 59 year old male with LNVUC whose tumour was initially misdiagnosed as a non-invasive low grade urothelial carcinoma. At a subsequent re-resection, his tumour was correctly re-classified as LNVUC with extensive invasion of the muscularis propria. Radical cystectomy and formation of an ileal conduit was performed. His operative specimen revealed invasion of prostatic stroma and perivesical fat, with all surgical margins clear. He is currently free from clinical recurrence 12 months after his cystectomy.

Conclusion
LNVUC is a newly described and rare urothelial carcinoma subtype. It characteristically possesses bland cytological features and may mimic low grade urothelial cancer. Despite its bland appearance it behaves aggressively with invasion, metastasis and death being common.

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Grant information: The author(s) declared that no grants were involved in supporting this work.
Competing interests: No competing interests were disclosed.
Introduction

The large nested variant of urothelial carcinoma (LNVUC) is a newly described variant of urothelial cancer (UC), with a single series of 23 cases being the only examples reported thus far\(^1\). This aggressive UC variant has deceptively bland cytological features, which may confound correct tumour classification. We present the case of a 59 year old male with a large bladder tumour who was initially diagnosed histologically as non-invasive low grade UC on initial resection. At re-resection the tumour was correctly identified as LNVUC.

Case report

A 59 year old Caucasian male was transferred to our unit from a regional hospital with a two week history of macroscopic haematuria. He sought medical attention only after he developed clot retention. He denied any previous history of haematuria or urinary problems prior to the two week period immediately before his hospital admission.

His medical history was unremarkable other than extensive carcinogen exposure, with both a 40 pack-year smoking history and significant occupational exposure, working as a fly-in, fly-out diesel fitter on a mine site.

On admission he required placement of an indwelling urinary catheter and continuous bladder irrigations. His initial serum creatinine was elevated, but soon normalised following catherisation. He was transferred to our secondary referral centre following failure of conservative therapies to control his persistent haematuria.

On his arrival to our facility we arranged Computerised Tomography (CT) to assess his bladder and upper renal tracts. CT demonstrated a grossly thick walled bladder with a large enhancing intra-vesical mass, and bilateral hydroureteronephrosis (Figure 1). His haematuria continued and he became transfusion dependant. He was taken to the operating theatre two days after his arrival for cystoscopic assessment.

At cystoscopy, there was a large papillary tumour involving the prostatic urethra, the trigone, and both lateral walls of the bladder. (Figure 2) Neither ureteric orifice was identifiable. The tumour was macroscopically resected after an extensive procedure.

Histologically the tumour was classified as a low grade urothelial carcinoma with no evidence of superficial or muscle invasion. We found this finding inconsistent with the operative and radiologic findings and repeated a cystoscopy four weeks later.

At repeat cystoscopy large volume tumour regrowth had occurred and a further 90 minute resection was performed. Tumour histology this time demonstrated invasion into the muscularis propria by a large nested variant of UC (Figure 3) with an adjacent superficial component of low grade papillary UC (Figure 4).

A staging Positron Emission Tomography (PET) CT was negative for metastatic disease and a cysto-prostatectomy and formation of an ileal conduit was performed. The operative specimen histology again revealed the large nested variant of UC with focal invasion into peri-vesical fat (Figure 5) and the prostatic stroma (Figure 6).

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Figure 1. Axial contrast enhanced CT demonstrating bilateral ureteric dilation (hollow arrows) and a large enhancing intravesical mass (solid arrow).

Figure 2. The bland appearance of the tumour at the bladder neck at his initial cystoscopy.

Figure 3. Low power view (×4 objective lens) of Hematoxylin and Eosin (H and E) stained bladder resection specimen showing the large nests of the invasive component of urothelial carcinoma with abundant interspersed stromal tissue.
A component of low grade UC was also present superficially. The tumour was clear of all operative margins. All lymph nodes sampled were negative for metastatic deposits.

The patient’s post-operative period was unremarkable and he made a swift recovery. He was discharged from hospital one week post-operatively. He was referred to medical oncology for consideration of adjuvant chemotherapy, however after discussion with oncologists the patient declined any additional treatment. He is presently twelve months post cysto-prostatectomy and he remains clinically well and free from clinical disease recurrence. We will continue to closely monitor this patient.

Discussion

The large nested variant is a newly described subtype of UC. The first and to date only case series was published in 2011 by Cox and Epstein and describes 23 cases\(^1\). They describe tumours with universally bland histologic appearances but with invasion of large nests resembling von Brunn’s nests into the underlying stroma. In contrast to the normal nested variant of UC, a surface papillary component is present and there is abundant fibrous stroma between individual tumour nests\(^1,2\). LNVUC is most commonly mistaken for low grade urothelial cancer with an inverted growth pattern\(^2\).

LNVUC behaves aggressively, of the 17 cases with adequate follow-up in Cox and Epstein’s series, 3 had died of their disease and another two were alive but had developed metastatic spread of their cancer\(^1\).

Conclusion

The large nested variant is an extremely rare, newly described variant of UC. Our case is only the 24th described in the literature, and the first case reported since the condition was first classified in 2011. LNVUC can confound accurate diagnosis by masquerading as Von Brunn’s nests or, in our case, low grade non-invasive UC. Despite the bland macroscopic and histologic appearance of LNVUC it behaves in an aggressive manner, and should be treated the same as any invasive urothelial malignancy.

Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contributions

AK was the author of the paper. AJL provided pathological input into the case report and provided images. AA contributed to writing of the article and was involved in proofing.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.
References


Open Peer Review

Current Referee Status: ✅ ✅ ✅

Version 1

Referee Report 02 February 2015
doi:10.5256/f1000research.6383.r7541

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This case report does an excellent job of highlighting the deceptive nature of LNVUC and the clinical importance of early detection. This aggressive and rare subtype of urothelial cancer can very easily be mis-diagnosed as a low-grade urothelial tumour. The article identifies the key demographic risk factors seen in LNVUC (male, heavy smoker, age- approx 60yrs) and highlights the clinical factors that point towards an aggressive pathology (upper tract dilatation, rapid regrowth). Early recognition is vital in allowing prompt radical treatment.

In our unit we have also had a very similar case of a bladder tumour which on resection was found to contain discohesive nests of invasive urothelial carcinoma. This patient also underwent radical cystectomy and final histology confirmed T3 disease.

As LNVUC can cause a diagnostic dilemma, we would be interested to learn if any immunohistochemical studies were carried out and what these showed.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 02 February 2015
doi:10.5256/f1000research.6383.r7138

Levent Turkeri
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This is a timely report on large nested variant of urothelial carcinoma. It may pose a diagnostic confusion since histological appearance may resemble more indolent forms of the disease although it certainly has a high invasive potential and may be associated with metastatic disease. Therefore, the pathologists must be aware of this variant when they evaluate surgical specimens and urologists must discuss with their pathologists the possibility of the presence of such a variant when they receive a report indicating low grade disease yet the clinical presentation is not compatible.
I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

**Competing Interests:** No competing interests were disclosed.

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Referee Report 07 January 2015

**doi:** 10.5256/f1000research.6383.r7134

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Nested variant of UC is indeed rarely reported. It is however, not certain whether the actual incidence is low or it is less frequently recognized. The estimated incidence is 0.3% (Hong et al., 2007).

Authors have correctly recognized the disparity in clinical parameters (Significant exposure, 40 pack year history, industrial exposure, large bladder growth and obstructive uropathy) with the pathology indicating low grade cancer (pTa LG). Most of the recognized clinical indicators of nested variant including male gender, age above 50 years, ureteral obstruction and cystoscopy showing tumor slightly raised and erythematous or nodular were present in this case.

I have few queries on which I request the authors to comments

1. Tumor is known to have aggressive behavior, however, growth in 4 weeks needing 90 minute resection is rather surprising.

2. Were any cold cup deep biopsies taken at the time of initial resection in view of the significant clinical findings of aggressive UC.

3. Were biopsies from the bladder neck, prostatic fossa or para collicular area taken at the time of initial resection.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

**Competing Interests:** No competing interests were disclosed.

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Author Response 07 Jan 2015

**Andrew Keller**, Ipswich General Hospital, Australia, Australia

Thanks for your review.

The described pathology in this case report is actually "large nested UC" which is a distinct clinical entity to "nested UC" and one only recently described. I agree that this entity, like "nested UC" is undoubtedly more common than is documented due to under reporting.

In regards to your queries.
1. I agree that the amount of tumour re-resection needed after only a 4 week interval following a macroscopically complete resection is surprising, it certainly was for us. One explanation is that a surgical trainee and not a consultant urologist was performing the resection, which would account for some of the additional time required.

2. No cold cup biopsies were taken at the time of the initial resection as the resection was felt to have adequately sampled the muscularis propria. Indeed, there was plentiful muscle present in the initial resection specimen histologically.

3. Cold cup biopsies were not taken from the bladder neck, prostatic fossa and paracollicular area at the time of the initial biopsies. However both bladder neck and prostatic fossa proximal to the prostatic utricle were involved with tumour at initial resection and these areas were consequently extensively resected with loop diathermy.

Thanks again for your comments and review.

Andrew Keller

**Competing Interests:** No competing interests were disclosed.