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Four Testicular Biopsies Failing to Detect a Case of Testicular Intraepithelial Neoplasia

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All testicular germ cell tumours (GCTs) develop through the precursor stage testicular intraepithelial neoplasia (TIN; also called carcinoma in situ). TIN is present in the testis many years before the clinical manifestation of the tumour (1, 2). Early detection of testicular cancer is possible by testicular biopsy with histological searching for TIN. The accuracy of the testicular biopsy to detect TIN is fairly high. The proportion of false-negative biopsies is reportedly in the region of 0.5% (3). Here we report on a case of testicular tumour that developed despite a total of four testicular biopsies being negative for TIN.

Case report. A 31-year-old man underwent left-sided inguinal orchiectomy for pure seminoma in another institution. No metastases were found, radiologically. Consecutively, the patient received prophylactic abdominal radiotherapy at a dosage of 26 Gy for a presumed clinical stage I seminoma. Contralateral biopsy had not been performed because the right-sided testicle had appeared normal upon palpation and ultrasonography, and, moreover, the patient's history was without any particular risk factor, e.g. history of cryptorchidism or familial testicular cancer. Two years later, a small hypoechoic intratesticular lesion was detected sonographically during follow-up (Fig. 1). Clinical examination and tumour marker analysis were normal, but magnetic resonance imaging (MRI) of the testis confirmed the presence of a small intratesticular mass at the cranial–dorsal site (Fig. 2). Consecutively, surgical inguinal exposure of the testis was performed. Surprisingly, no tumour could be identified despite intensive intraoperative palpation and ultrasound imaging. To rule out malignancy, a small specimen of testicular tissue was excised from the presumed location of the suspected neoplasm and, in addition, a total of three testicular biopsies were taken from different parts of the testicular parenchyma. The surgical procedure was then terminated. Recovery was uneventful. All four of the biopsy specimens had been fixed in Stieve's solution and all of them were larger than 3 mm in diameter. Immunohistological examination involving staining of placental alkaline phosphatase (PLAP) was negative for TIN in all of the specimens. Upon re-examination one year later, the intratesticular mass had slightly increased in size, both sonographically and by MR imaging (Fig. 3). Repeat surgical exploration now disclosed a tiny palpable tumour located close to the rete testis. Partial orchidectomy was performed with preservation of the right

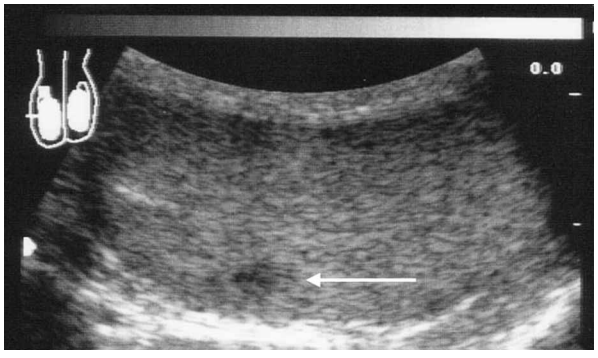

Fig. 1. Sonographic image (7.5 Mhz) of the right testis obtained two years after left-sided orchiectomy. Notice the small hypoechoic intratesticular mass (arrow).

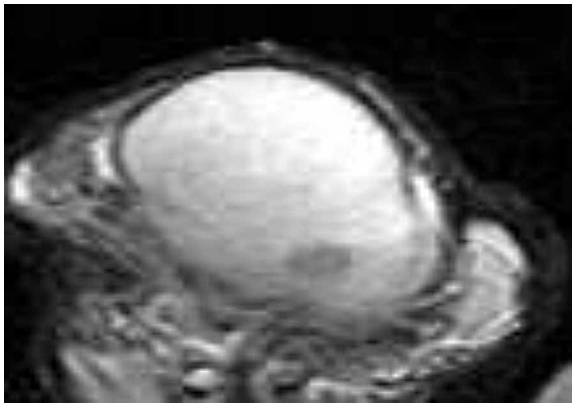

Fig. 2. MRI imaging of the right testis obtained two years after left-sided orchiectomy. 1.5 Tesla MRI machine (Philips). T2-weighted image. Notice the small intratesticular mass with low signal intensity. This image corresponds exactly to the sonographic view. Intraoperatively, this mass was missed.

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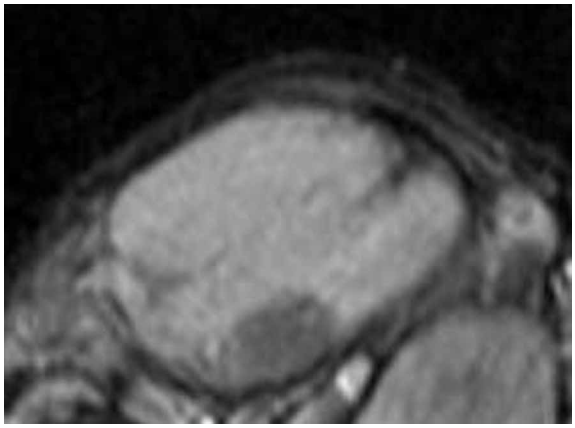

Fig. 3. MRI imaging, right testis, three years after left-sided orchiectomy, one year after surgical evaluation of this testicle. T1-weighted image, fat suppression, contrast media application. The intratesticular mass has gained in size. Repeat surgery now reveals solid seminoma.

testicle. Histological examination of the excised tumour revealed pure seminoma measuring 10 mm in diameter (Fig. 4). What is noteworthy is that there was evidence of scattered TIN cells in the testicular parenchyma surrounding the neoplasm (Fig. 5). The patient underwent postoperative radiotherapy of the testis at a dosage of 20 Gy to eradicate TIN. Again, one year later, the patient is well clinically with no signs of local or distant tumour recurrences.

Comment. This case is of note because a total of four testicular biopsies were falsely negative for TIN. When the principle of searching for TIN was introduced into clinical medicine in 1980, Berthelsen & Skakkebaek had hypothesized that TIN is a disperse lesion throughout the testicle (4). Consecutively, a solitary randomly directed testicular biopsy was thought to be representative for the entire testicle. In fact, development of testicular germ cell tumours despite a previously negative biopsy for TIN is rare. To date, no more than 44 cases with a false-negative biopsy for TIN have been reported and the proportion of a failed diagnosis of TIN is estimated to be in the range of 0.5% (3). The chief reason for

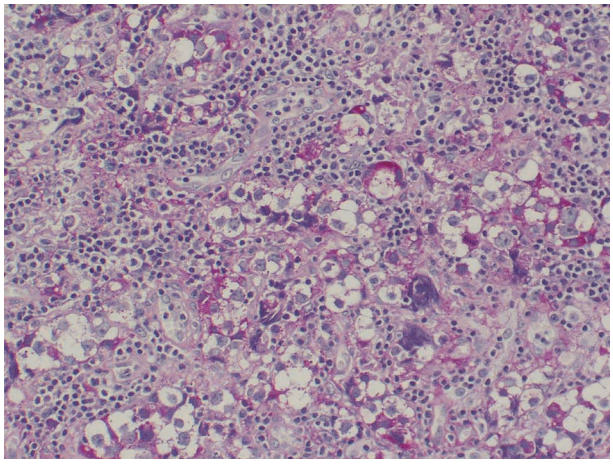

Fig. 4. Histological section of the resected intratesticular mass. Typical invasive seminoma with lymphocytic infiltration. PAS stain. Original, $\times 400$.

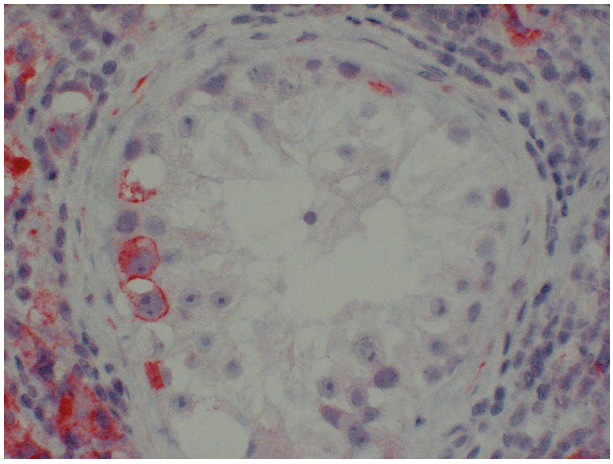

Fig. 5. Immunohistological section. Seminiferous tubule in tumour-surrounding tissue containing several TIN cells located at the basement membrane (stained red). PLAP, original, $\times 400$.

missing the diagnosis of TIN by testicular biopsy is the non-random distribution of TIN within the testicle. In contrast to the old hypothesis of Berthelsen & Skakkebaek, it is undisputed today that TIN is a focal lesion during long periods and that it spreads within the testicular lobules and leaves other parts of the testicular parenchyma unafflicted (5). Consequently, random biopsies that fail to detect TIN must be expected. Thus, patients with known risk factors for bilateral testicular cancer, e.g. cryptorchidism, familial testis cancer, testicular atrophy, probably benefit from thorough clinical follow-ups even in the presence of a negative biopsy for TIN.

In the event of a sonographically proven intratesticular neoplasm, a sonographically directed biopsy to aspirate tissue from the region of interest appears principally feasible. However, this manoeuvre is rarely employed because it is hampered by several practical difficulties. One key problem is that the testicle needs to be in a fixed position to allow accurate directing of the aspiration needle.

Recently, efforts have been made to improve the diagnostic safety by taking two-site biopsies. Expectedly, a significant number of cases were found where only one of the two biopsies was positive for TIN. Also expectedly, no case with a false-negative double biopsy has been observed so far (6). Thus, the present case is unique because even a total of four testicular biopsies had failed to detect TIN. The contralateral seminoma reported here developed from the precursor TIN in accordance with the well-known histogenetic theory of testicular germ cell neoplasms. This conclusion is based on the evidence of TIN cells in the vicinity of the tumour. However, in contrast to the vast majority of germ cell tumours, only very few TIN cells were found in the testicular tissue adjacent to the tumour (Fig. 5). Accordingly, it must be assumed that only a few precursor cells had been present in that testicle before manifestation of the clinical tumour. Even in light of this interpretation, it is still surprising to have four full-load biopsies taken from different compartments of the testicle, all of them actually failing to detect TIN.

Obviously, the lesson to be learned from this case is that TIN may sometimes be hidden in remote compartments of the testis. Even a small number of TIN cells can give rise to full-blown testicular cancer. The observation that TIN was overlooked in even four biopsies prompts us to remember the general experience with clinical medicine: that even procedures thought to be extremely safe may fail in exceptional cases.

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