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EDITORIAL

Sertoli cell only revisited

Intracytoplasmic sperm injection (ICSI) has made the most severe cases of oligoasthenoteratozoospermia treatable. The presence of only a few weakly motile spermatozoa in a centrifuged ejaculate are sufficient to produce results equivalent to that of in-vitro fertilization (IVF) in couples with completely normal semen (Van Steirteghem *et al.*, 1993a;b). In obstructive azoospermia, ICSI with epididymal, and even testicular biopsy-extracted spermatozoa, gives pregnancy rates equivalent to that of normal ejaculated spermatozoa from a fertile male (Devroey *et al.*, 1994; Silber *et al.*, 1994, 1995). Extensively applying these techniques, we have now found that even in men with apparently absent spermatogenesis, who have complete azoospermia, with no spermatozoa even in the centrifuged semen, there is none the less commonly a small amount of sperm production to be found somewhere in the testicles.

'Sertoli cell only' syndrome was first described by del Castillo *et al.* (1947). It is characterized by total azoospermia (even after centrifugation) and a testis biopsy showing complete absence of germ cells, with only normal Sertoli cells lining the seminiferous tubules, and somewhat small testes and normal androgenization. There was no history in any of these patients of any diseases or conditions (such as cryptorchidism or mumps) that 'could have been harmful to the germinal epithelium'. In the subsequent 47 years 'Sertoli cell only' syndrome has become recognized as the most common cause of non-obstructive azoospermia in 'sterile' males.

'Maturation arrest' is characterized by normal-sized testicles and normal androgenization, but complete failure of reduction division, or meiosis, of tetraploid pachytene spermatocytes to haploid spermatids (Amelar, 1966; Colgan *et al.*, 1979; Micic *et al.*, 1983; Nagpal *et al.*, 1993). It is the next most common cause of non-obstructive azoospermia in 'sterile' males. Together, 'Sertoli cell only' and 'maturation arrest' are (with a few occasional exceptions) the only conditions for which ICSI has seemed to be of no use, because of the impression over the years that these conditions meant absolute spermatogenic failure.

It is now clear, as demonstrated in Figures 1–4, that if the entire testis is carefully sampled, more than half the cases of 'Sertoli cell only' syndrome will have occasional foci of normal seminiferous tubules with spermatogenesis. All of the patients from whom the samples were taken for the figures had azoospermia, elevated follicle stimulating hormone concentration and no spermatozoa visible in the centrifuged ejaculate. In fact, there are often foci of maturation arrest in testes with 'Sertoli cell only', and likewise there are foci of 'Sertoli cell only' in testes that show predominantly maturation arrest. For many reasons, it has been postulated that these conditions are genetic in origin and may be different expressions of the same isolated genetic defect in spermatogenesis.

It is evident that these defects are not usually total, as was formerly thought (as indicated by the name 'Sertoli cell only'). In more than half of these cases a careful search throughout the testicle in such patients will often yield occasional spermatoza. The numbers produced (in the range 0–100 to as many as 10 000) are obviously too small to reach the ejaculate in most cases, but that does not mean spermatozoa are absent from the testes.

In our original studies on quantification of spermatogenesis

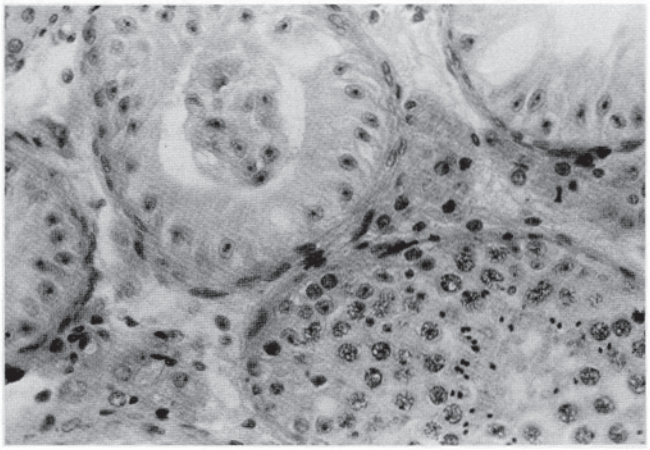

Figure 1. Top two seminiferous tubules demonstrate 'Sertoli cell only' in a patient whose testicle was almost exclusively 'Sertoli cell only' except for the tubule on the bottom right that has normal spermatogenesis.

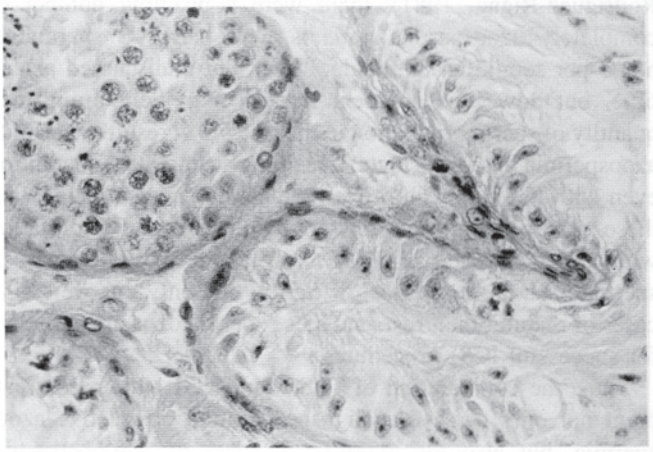

Figure 2. Another patient with predominantly 'Sertoli cell only' has a single tubule showing normal spermatogensis next to typical 'Sertoli cell only'.

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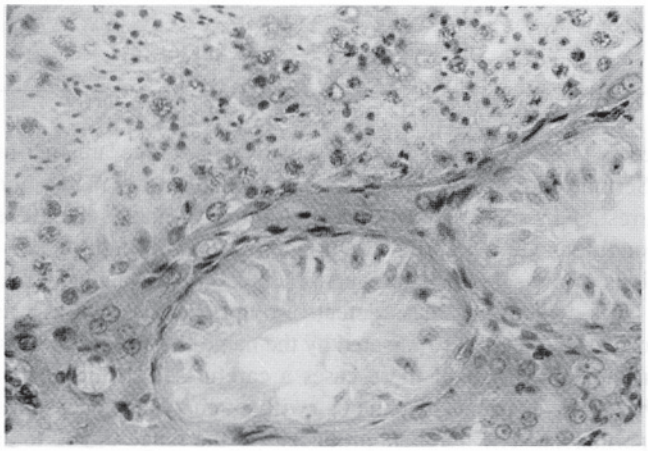

Figure 3. A patient whose first testicle biopsy showed 'Sertoli cell only'. A repeat biopsy demonstrates a small focus (upper longitudinal tubule) of normal spermatogenesis.

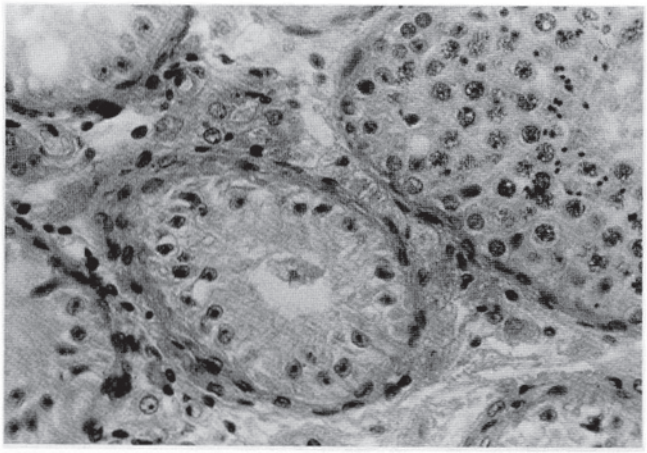

Figure 4. A patient with supposedly exclusively 'Sertoli cell only' who shows again one tubule, upper right, with normal spermatogenesis.

upon histology in comparison with sperm count (Silber and Rodriguez-Rigau, 1981), there were a puzzling number of completely azoospermic patients who had 1–2 spermatids noted per seminiferous tubule. This went undiscussed at that time, but now it is apparent that an extremely diminished quantity of sperm production in the testes will result in absolute azoospermia in the ejaculate, a seemingly untreatable condition even with ICSI. Now, however, the pessimism associated with these conditions appears unwarranted. Testicular exploration with sperm extraction (TESE) can yield small numbers of spermatozoa in most cases of 'Sertoli cell only', as well as in cases of maturation arrest, and these spermatozoa are sufficient for successful ICSI procedures.

Thus, the combination of TESE and ICSI allows the treatment not only of severe oligospermia and obstructive azoospermia, but also the majority of cases of non-obstructive azoospermia. A similar approach to solving the problem of non-obstructive azoospermia that would not require the sacrifice of testicular tissue is to first vasectomize such men, in order to allow epididymal storage of these rare spermatozoa. Then microsurgical aspiration of spermatozoa (MESA) could be performed in preference to TESE. Either way, it is clear that spermatozoa can be surgically retrieved from most men who appear to be making no spermatozoa. Thus, whenever the ejaculate is not adequate for ICSI, TESE or MESA should be considered.

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