

Intratubular Germ Cell Neoplasia in the Pediatric Population: A Case Report

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ABSTRACT

Testicular cancer, specifically germ cell tumors, are the most common malignancy in young men and are curable in up to 95 % of cases, but the incidence is on the rise. The key event in the transformation to malignancy is hypothesized to occur in early adulthood, and the carcinogenic pathway for germ cell tumors is thought to begin in fetal life due to maternal or environmental estrogen exposure. Intratubular Germ Cell Neoplasia (ITGCN), previously known as Carcinoma in Situ (CIS) of the testis, is a premalignant condition that can progress to testicular cancer and is associated with testicular germ cell tumors. ITGCN is rarely reported in prepubertal children, and it would be helpful to know the prognostic implications of this finding. We present a case report of a 4-month-old male with undifferentiated ITGCN, and a co-morbid mature teratoma, one of only a few cases currently published. This patient had a normal 46, XY karyotype and all normal laboratory result except for a slightly elevated AFP, which is considered a normal finding for his age. Our report contributes to the growing body of evidence of ITGCN in the pediatric population and how little is known about this diagnosis. We will also briefly review management options for these patients and how we will be following this patient.

KEYWORDS: *intratubular germ cell neoplasia, testicular carcinoma in situ, pediatric testicular tumors, germ cell tumor, prepubertal testis*

INTRODUCTION

Testicular cancer, specifically germ cell tumors, are the most common malignancy in young men and are curable in up to 95 % of cases, but the incidence is on the rise.¹ The key event in the transformation to malignancy is hypothesized to occur in early adulthood, and the carcinogenic pathway for germ cell tumors is thought to begin in fetal life due to maternal or environmental estrogen exposure.¹ Intratubular Germ Cell Neoplasia (ITGCN) is a pre-neoplastic lesion for testicular cancer. Testicular cancer has its peak incidence in men ages 20-40 years old and is associated with the following risk factors: cryptorchidism, early puberty, family history of testicular cancer, and those with genetic syndromes such as Klinefelter's syndrome (47, XXY karyotype).² Germ cell tumors, a subset of testicular cancers, are four to five times more common in white males than African-American males and those from Scandinavia or New Zealand appear to have a higher risk than those in America.³

If an imbalance in normal germ cell division occurs, then abnormal cells can develop into ITGCN, a pre-malignant

lesion. Several genetic abnormalities have been reported to be associated with ITGCN, with isochromosome 12p reported in all adult patient cases of ITGCN.^{2,4} In germ cell tumors diagnosed in infants and young boys, however, isochromosome 12p has not been observed.⁵

Microscopically, ITGCN shows neoplastic cells in a thickened basement membrane within the seminiferous tubules.⁴ The seminiferous tubules do not show evidence of spermatogenesis in cases of ITGCN.⁴ The WHO classifies germ cell tumors of the testis into several categories including "precursor lesions," "tumors of one histological type," "tumors of more than one histological type," and "sex cord/gonadal stromal tumors."⁶ Precursor ITGCN lesions are further divided into "unspecified," "intratubular embryonal carcinoma," and "intratubular seminoma" categories.⁶

CASE REPORT

We present a case of a 4-month-old male who was presented to the hospital after his mother noticed swelling of his right testicle. This patient had no significant past medical or family history. The testes were reported to be normally descended at birth, with no palpable masses.

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CASE AND ELECTIVE REPORTS

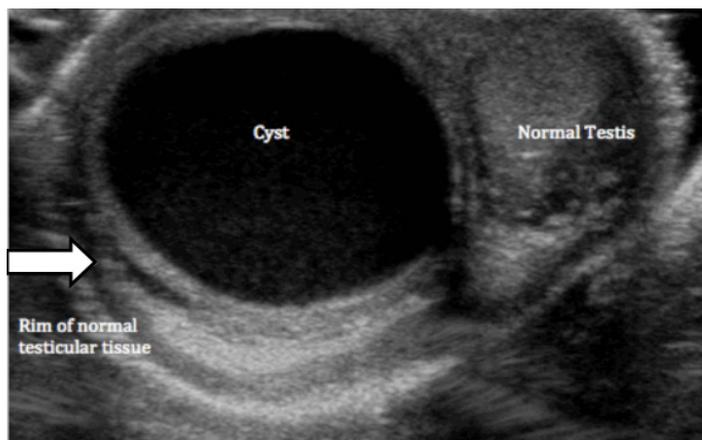


Figure 1. Transverse ultrasound of testicles showing a large fluid filled cyst with a rim of normal testicular tissue and one normal testicle.

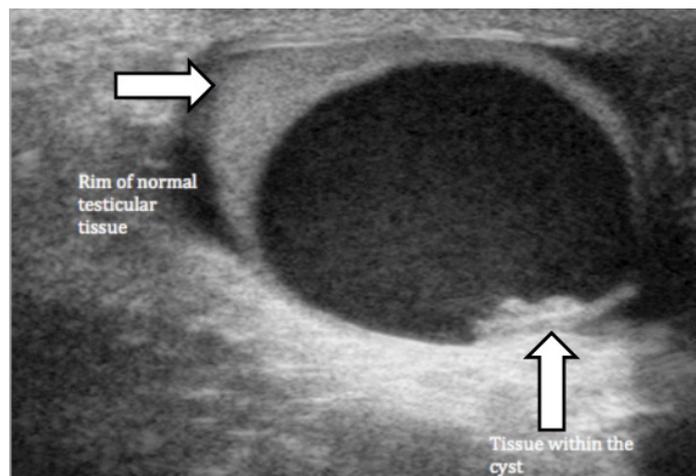


Figure 2. Transverse ultrasound of affected testis showing the large fluid filled cyst, the rim of normal testicular tissue and tissue within the cyst, perhaps an old hemorrhage.

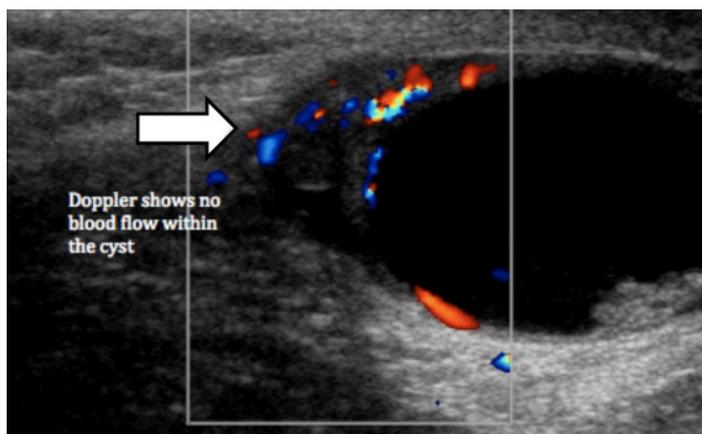


Figure 3. Color doppler of affected testis showing no blood flow into the cyst making the lesion less likely to be a malignancy as a malignancy would need a blood supply.

SOAP Note

Subjective

- 4 month old male presents to hospital after mother noted swelling of right testicle
- No significant past medical history
- No significant family history
- Normally descended testes at birth

Objective

- Enlarged right testis, normal left testis
- U/S revealed large cyst in lower pole of right testis that measured 2.1cm X 2.2cm X 2.8 cm
- Right testis measured 2.6cm long
- Mural nodule within the cyst
- Epididymis appeared normal on both sides
- CBC, biochemistry unremarkable
- AFP 33ug/L
- Beta HCG <1.2 U/L (N <5 U/L)
- Pathology results from mass showed a mature teratoma with adjacent seminiferous tubules containing intratubular germ cell neoplasia

Assessment

- History, pathology and labs confirm intratubular germ cell neoplasia

Plan

- Partial resection if possible, total orchiectomy if not enough testicular tissue
- Total orchiectomy was performed
- Continue to follow with imaging, laboratory values (AFP and beta HCG) and clinical exams to ensure a germ cell tumor does not develop

After an unremarkable physical exam except for the enlarged right testis, he underwent an ultrasound. The ultrasound revealed an unremarkable left testis and epididymis, with the testis measuring 1.5 cm in length with a normal color Doppler. His right testis showed a large cyst within its lower pole, and the impression of a mural nodule within the cyst. The epididymis appeared normal. The testicular tissue around the cyst had normal Doppler color flow and there was no evidence of a hydrocele. The cyst measured 2.1 cm x 2.2 cm x 2.8 cm and the testis measured 2.6 cm long. The initial impression after the ultrasound was that of a cyst of the right testis with the possibility of a soft tissue mass.

Blood work was carried out, including a CBC and serum biochemistry, and was unremarkable. The serum Alpha Fetoprotein was 33 ug/L, which was above the standard reference range but consistent with the knowledge that infants have higher levels of AFP until 8 months of age, after which they begins to approach adult levels.⁵ A beta HCG was also done and it was normal at less than 1.2 IU/L (N<5 IU/L). Common testicular tumors in this age group are the yolk sac tumors which lead to elevated levels of AFP in 50-70% of testicular germ cell tumors.⁴ Beta HCG is elevated in tumors which contain syncytiotrophoblastic cells and is elevated in 50% of germ cell tumors.⁴ Therefore, normal values of these proteins do not rule out disease but rather make it less likely and need to be combined with pathology to reach a diagnosis, as was done in this case.

Surgery was performed five days later with the operative plan to do a partial orchiectomy or a radical orchiectomy if a partial resection was not possible. At surgery it became obvious that there was no normal testicular tissue on the right side, and a right radical orchiectomy was performed. The final pathology report revealed a mature teratoma, with adjacent seminiferous tubules containing ITGCN. The cells also stained CD117 positive, indicating the presence of a cytokine receptor that is abnormally expressed by germ cells in ITGCN.⁶ PLAP staining was not done as it has been replaced with CD117 testing in our pathology department and PLAP may not be a reliable marker for ITGCN in prepubertal testis.⁷

This patient was then referred to our pediatric oncology service. Further staging work-up, including a CT of the chest,

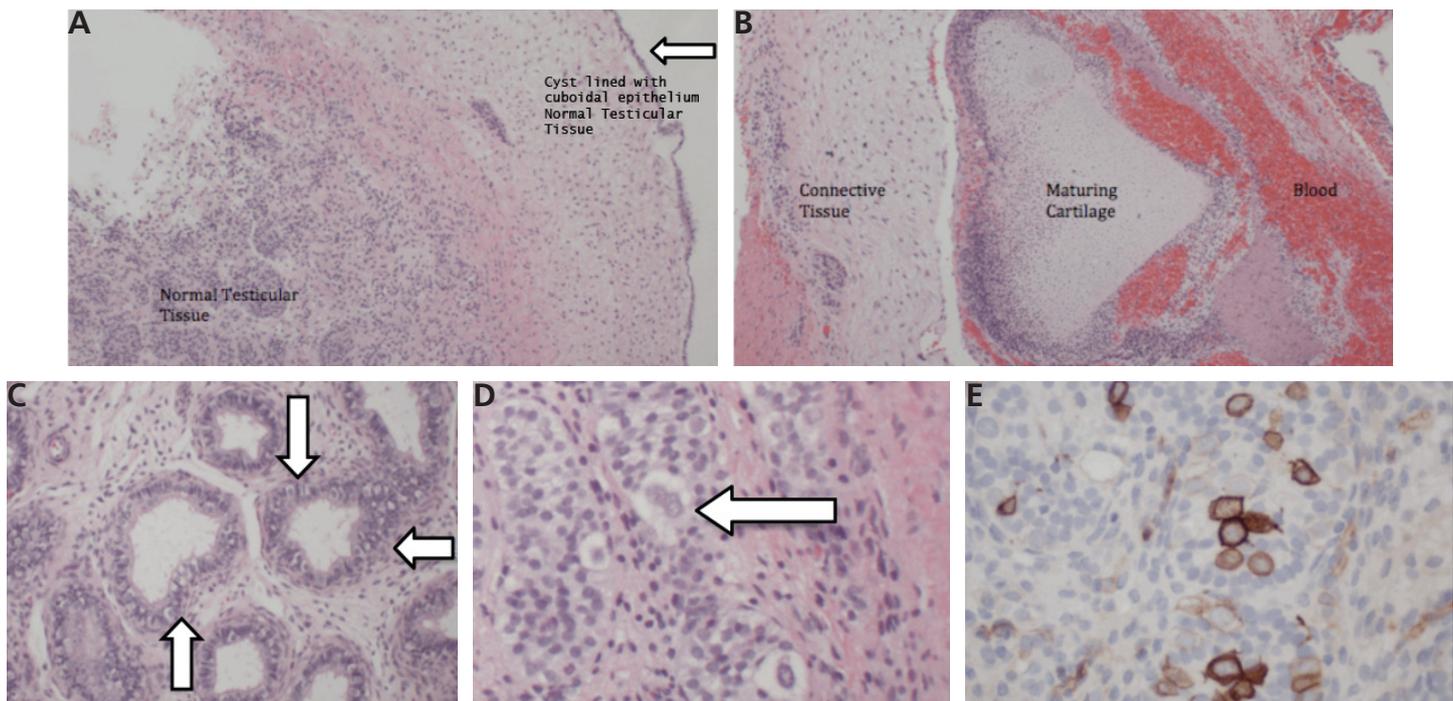


Figure 4. (A) Cyst with cuboidal cell lining and normal testicular tissue in the centre. 10X H&E. (B) Teratoma showing maturing cartilage, connective tissue and blood. All 3 embryonal layers were not in this section. 10X H&E. (C) Intratubular germ cell neoplasia as indicated by the classic large clear cytoplasm filled with glycogen, "pearls on a string." 20X H&E. (D) Intratubular germ cell neoplasia with multiple cells that are binucleated and large glycogen filled cytoplasm with atypical nuclei. 40X H&E. (E) Positive Cytokine CD117 stain. CD 117 is a cytokine receptor expressed by germ cells and stem cells during fetal life, and is positive in ITGCN as these are abnormal, potentially protooncogenic cells. 40X CD117 stain.

abdomen and pelvis, was done and showed no evidence of metastatic disease. Karyotyping was also requested and showed a normal 46 XY karyotype, without evidence of isochromosome 12p. Regular follow-up appointments were arranged for this patient in the Oncology Clinic every six months with an abdominal ultrasound, BHCG and AFP levels being monitored. After two to three years the follow up will change to yearly. There are currently no recommendations in the literature to guide follow up so our approach is extrapolated from follow up guidelines for pediatric patients with germ cell tumors.⁸

DISCUSSION

ITGCN is well recognized in the adult population as a precursor to testicular germ cell tumors for the following three reasons:

1. ITGCN is found in the same population as those at risk for testicular germ cell neoplasia;
2. When found in adult testicular biopsies approximately 50 % will develop an invasive form of testicular germ cell tumor within five years;
3. ITGCN is found in seminiferous tubules adjacent to testicular germ cell tumors in approximately 82.4 % of adult cases.^{6,9}

After an extensive literature search, only a few cases of ITGCN in an infantile testis have been reported.^{7,10} A review of 25 ITGCN cases by Guinand and Hedinger did not reveal any cases in pediatric patients.¹¹ Hu et al described another case of ITGCN however this was next to a yolk sac tumor not a mature teratoma as was in our patient.¹² Other infantile cases of ITGCN are commonly associated with cryptorchidism, however this result is not always the case as demonstrated by Parkinson et al.¹³

In the adult population, a benign teratoma associated with the presence of ITGCN carries a recognized risk of progression to malignancy.⁵ However, due to the paucity of reported cases in children, risk of progression to a malignancy in the pediatric patient is not known. Monitoring of these patients, as is performed for adult patients with this diagnosis, must therefore be recommended until further information is known about the natural history of this condition in children.

For our patient, a radical orchiectomy was undertaken as testis sparing surgery was not felt to be possible. As the testicle was completely removed, with negative margins, it was felt that no further ipsilateral surgical management was required.

The question of whether or not to biopsy the contralateral testicle remains. Review of the literature does not provide any justification for biopsy as germ cell tumors in infants and children are very rare, so the chance of another ITGCN is extremely unlikely.¹⁴ Also, if the biopsy showed ITGCN, it cannot be known if a subsequent orchiectomy would be the correct course of action given the uncertain malignant risk for ITGCN in this patient population and the significant morbidity of such an operation in terms of sterility and lifelong hormone replacement. Given these considerations we have elected to follow the patient closely at six month intervals with abdominal ultrasound and blood work for the first 2-3 years and then yearly for any evidence of recurrent or contralateral disease.

Should a prepubertal patient with normally descended testes present with a diagnosis of ITGCN made by incisional biopsy only, the literature does not provide any guidance for further surgical or oncologic management.

CONCLUSION

Intratubular germ cell neoplasia is a rare finding in children, and carries an unknown risk for future malignant change. Currently there is no evidence to guide treatment and follow-up of patients presenting with this unusual pathologic finding. Extrapolating adult experience may not be useful, as children tend to have different genetic findings. For our patient, we chose to augment follow up guidelines for pediatric patients with germ cell tumors. More data on the incidence of ITGCN in children is needed to assess the my, risk factors, and potential benefits.

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Homeopathy as an Adjunct to Allopathic Therapy

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ABSTRACT

More and more patients are seeking alternative medical therapies, and in order to provide the best possible care for our patients, it is our responsibility to learn about the variety of options out there that patients may choose to seek out in order to improve their health. In the following article I aim to recount my experiences during my third year elective in homeopathy. Homeopathy dates back about 200 years, when Dr. Hahnemann proposed the “Law of Similars”—the basic tenet of homeopathy. All homeopathic remedies are based on this law and are produced via the process of potentization—repeated dilutions and succussions of a substance, usually until there is no active ingredient remaining. The remedies are selected by matching their known symptoms with the characteristic symptoms of the patient. Homeopaths consider not only the current symptoms but also constitutional symptoms such as the patient’s personality, temperament, and his or her social, occupational, and family history. Homeopaths spend a considerable amount of time with new patients in order to get a complete history, and these long consultative sessions are a definite benefit of homeopathy. After spending some time in this elective, I believe that homeopathy could be a welcome adjunct to allopathy in order to provide patients with the most comprehensive care possible.

KEYWORDS: *alternative medicine, homeopathic medicine, homeopathy*

During my rural family practice rotations this summer, I found that many patients asked whether my preceptor or I recommended homeopathy for their various chronic conditions. Neither of us was able to give a helpful answer because alternative medicine is not very well covered in the

allopathic medical curriculum. This experience prompted me to spend my third year elective working with a homeopath in order to learn about the theory behind homeopathy and the treatments used within this field. More and more patients are starting to seek alternative medical therapies, so I thought it would be valuable to share what I learned during this elective with future allopathic practitioners. This information may help them understand if and

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