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Recurrent ovarian immature teratoma in a 12-year-old girl: Implications for management

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ABSTRACT

Immature teratomas (IT) are rare and recurrences uncommon. A 12-year-old female with grade 3 (high-grade) ovarian IT underwent surgical resection but experienced early recurrences; the first was treated with surgery but the second was metastatic and managed with chemotherapy, resulting in growing-teratoma-syndrome and need for further surgery. She now remains well in uneventful clinical follow-up. We believe chemotherapy could be reserved for very carefully selected recurrent IT cases, which may alter the natural history of disease.

1. Presentation of the case

A 12-year-old girl presented to her family doctor with a distended abdomen and two-month history of intermittent lower abdominal pain. Other symptoms included lethargy and anorexia. Menarche was noted six months prior to this with no abnormal or irregular bleeding. She was referred to the local pediatric department. Investigations revealed a raised serum alpha-fetoprotein (AFP) of 183 kU/L (Fig. 1). Abdominal ultrasound scan (USS) showed a large, complex cystic mass arising from the right ovary with associated hydronephrosis of the right kidney. Referral was made to a specialist tertiary pediatric oncology care, where an MRI confirmed the presence of a 30 cm diameter complex right ovarian cyst which contained areas of fat; no extra-ovarian spread was identified (Fig. 2A/B).

The patient underwent surgery. Due to the large size of the lesion, laparoscopic surgical drainage of 4.7 L of lesional fluid was undertaken first to facilitate surgical resection (Fig. 2A/B). Laparotomy and right salpingo-oophorectomy were then performed intact, which included removal of the mass arising from the right ovary. Omental biopsy was also performed. The left fallopian tube and ovary appeared macroscopically normal. Histology showed an immature teratoma (IT) of Norris [1,2] grade 3 (high-grade) (Fig. 3A) with microfoci of yolk sac tumor (YST) termed 'Heifetz' [3] lesions. The sampled omentum was histologically normal. Save for the multiple microfoci of YST, no additional malignant germ cell elements were identified. Peritoneal fluid cytology was negative. Consequently, overall staging (according to revised FIGO criteria) [4] and grading was concluded as stage 1C1 (due to surgical aspiration) high-grade IT. After surgery, surveillance AFP levels returned to within the normal range within two months (Fig. 1) and MRI showed no recurrence.

Five months following surgery, the serum AFP level had risen again to 176 kU/L and the patient reported a short history of occasional abdominal and lower back pain. An MRI revealed a large heterogeneous solid and cystic pelvic mass filling the pouch of Douglas, with small volume ascites (Fig. 2C) and subsequently serum AFP estimations increased rapidly to 1035 kU/L (Fig. 1). Consistent with the published literature for pediatric IT [5,6], discussion with national and international experts led to the decision to offer surgery with the aim of total resection, if feasible. Laparotomy was therefore undertaken; at operation the findings were of an 8 × 6 cm recurrence in the omentum and a small deposit on the otherwise normal remaining left ovary which was biopsied and shown to be a corpus luteum. An infracolic

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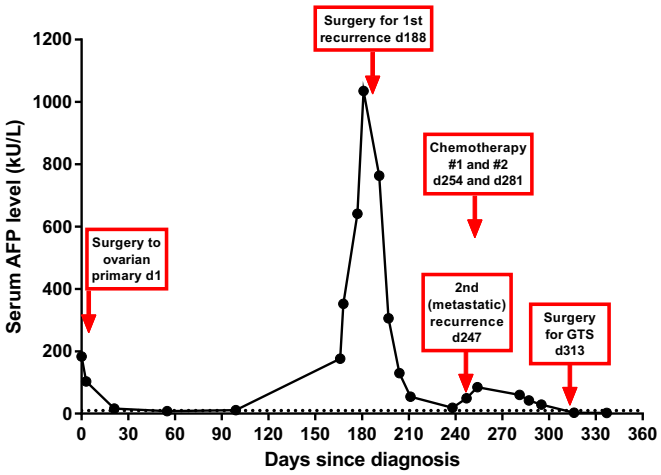

Fig. 1. Longitudinal serum AFP estimations for the ovarian immature teratoma case. Interventions (boxes) are shown at the specific timepoints indicated by the red arrows. Key: d = day; GTS = growing teratoma syndrome; # = chemotherapy course.

omentectomy was performed with complete macroscopic clearance of disease. Histology once again showed a grade 3 (high-grade) IT (Fig. 3B) with multiple microfoci of YST (Fig. 3C) again present; the microfoci stained positively for AFP (Fig. 3D) and glypican-3 (Fig. 3E). Some of these foci were >2 high power fields (HPF) in size, giving a histologic differential diagnosis of high-grade IT with YST microfoci or mixed malignant GCT. Peritoneal fluid cytology was again negative. Following extensive MDT discussion, a grade 3 (high-grade) IT with YST microfoci diagnosis was favored and hence a further close 'watch-and-wait' approach was adopted. Three days post-operatively, the serum AFP level had fallen to 763 kU/L and one month later it was 19 kU/L (Fig. 1).

Two months after her second surgery (and eight months after initial presentation), a follow-up MRI revealed 15 × 27 mm right-sided adnexal disease (Fig. 2D) and a new 11 mm diameter parenchymal liver lesion (Fig. 2E) consistent with metastasis via haematogenous spread. At the same time, the serum AFP level had risen modestly to 49 kU/L (Fig. 1). After further discussion with national and international experts, due to the metastatic nature of the disease, she was commenced on carboplatin, etoposide and (once per cycle) bleomycin ('JEb' or 'CEb') chemotherapy. After two cycles, routine reassessment MRI demonstrated that the lesions had increased in size (Fig. 2F). Chemotherapy was discontinued, and a laparotomy performed, which included a partial hepatectomy (non-anatomical segment 6/7 liver resection) and resection of pelvic adnexal disease (one small lesion anterior, and one larger lesion posterior, to the uterus). Pathologic examination showed that the lesion posterior to the uterus was a low-grade IT, whilst the lesions in the liver and anterior to the uterus were mature teratoma (MT) (Fig. 3F). After surgery, the serum AFP level fell to normal (<10 kU/L) and MRI confirmed no evidence of recurrent disease. The patient remains clinically well 18 months after her most recent surgery, with serial AFP estimations and MRI appearances within normal limits.

2. Epidemiology and presentation of ovarian immature teratoma

In the pediatric population, ovarian teratomas, a subtype of GCT, are the most common type of ovarian tumor [7], but in gynecologic oncology practice, they make up only a small percentage of ovarian cancer cases [8,9]. They are divided into MT and IT. Histologically, MT are made up of mature tissues of ectodermal, mesodermal and endodermal origin; IT are also composed of tissues from these three germ cell layers, however they display additional immature elements (Fig. 3) [6]. MT is the most common form and typically presents in women aged between 20 and 40 years; this form of teratoma is generally considered benign, although somatic malignancies such as sarcoma may arise from the constituent components [10]. IT is rarer and tends to present in those under 20 years old, peaking in incidence in patients between 15 and 19 years of age [11]. IT may present as a pelvic mass, abnormal uterine bleeding, abdominal pain or abdominal distension [7,12]. AFP levels are often raised at diagnosis (Fig. 1) and may be useful to monitor for recurrence. This may be due to AFP production from 'microfoci' of YST, termed Heifetz lesions [3], within the IT, or from other immature gastrointestinal or liver components within the mass [13].

3. Imaging characteristics in ovarian immature teratoma and recurrence

Imaging generally shows IT as a large ovarian lesion with complex features. They are heterogeneous on both CT and MR imaging and have predominantly solid components with smaller cystic areas (Fig. 2). They typically contain small areas of fat and scattered calcification. The detection of punctate areas of fat among a large solid lesion on imaging is therefore very helpful in raising the possible diagnosis of IT. This is in contrast to MT, which usually contain much larger areas of fat and the calcification is 'tooth-like'. The larger amount of solid tissue and heterogeneity in IT is helpful in distinguishing from MT and also from other malignant GCT subtypes such as dysgerminoma and YST, which also often present as large solid ovarian masses, but which do not show the punctate fat containing areas.

Recurrent disease typically occurs within the pelvis at the site of original tumor (Fig. 2). Recurrence may be small volume and multifocal, which is challenging to detect on imaging. This is particularly the case in the pelvis following surgery, where there is often associated post-surgical change and fibrosis. Generally, recurrent disease looks similar in appearance to imaging at initial presentation, with a heterogeneous soft tissue focal lesion. Given the peritoneal spread of ovarian disease, the surface of the liver and spleen are important areas to assess for subcapsular deposits. These are seen at the periphery of the liver or spleen and extend in subcapsular formation as a focal lesion. Peritoneal gliomatosis is due to the formation of mature glial cells which on imaging appears as peritoneal thickening, particularly around the liver and hemidiaphragms and within the pouch of Douglas. This finding mimics peritoneal disease from recurrent IT disease and unfortunately is not distinguishable on imaging alone. In such cases, AFP estimation may also help to distinguish peritoneal gliomatosis (normal levels) from peritoneal IT disease (where levels are often elevated) [14]. Serial imaging of these patients is helpful, which in patients with peritoneal gliomatosis may demonstrate stability, whereas IT recurrence often progresses rapidly.

4. Pathology and molecular characteristics of ovarian immature teratoma

As highlighted above, ovarian teratomas are classified by the World Health Organization (WHO) as MT and IT [15]. In adult practice, IT are often considered malignant lesions, but this is generally not the case in pediatric practice [5,6]. IT have the potential in a small proportion of cases to exhibit behavior more consistent with malignant GCT subtypes, such as metastasis; this property may be linked to certain histologic markers [7]. German groups suggest that it is the presence of the microfoci of YST ('Heifetz' lesions) that confer malignant potential to IT [16], but this hypothesis was not borne out by a large UK pediatric series [5] and therefore remains a controversial area [5,7]. There is no absolute definition of what constitutes microfoci in terms of diameter of these Heifetz lesions. In this case, we followed the guidance of Mann et al and reported microfoci when one or more was seen, each occupying not more than two adjacent HPFs at ×40 microscopic objective [5].

IT are defined as teratomas containing variable amounts of immature, embryonal-type tissue (mainly neuroectodermal tubules and rosettes) (Fig. 3). The primitive neuroepithelial cells are hyperchromatic

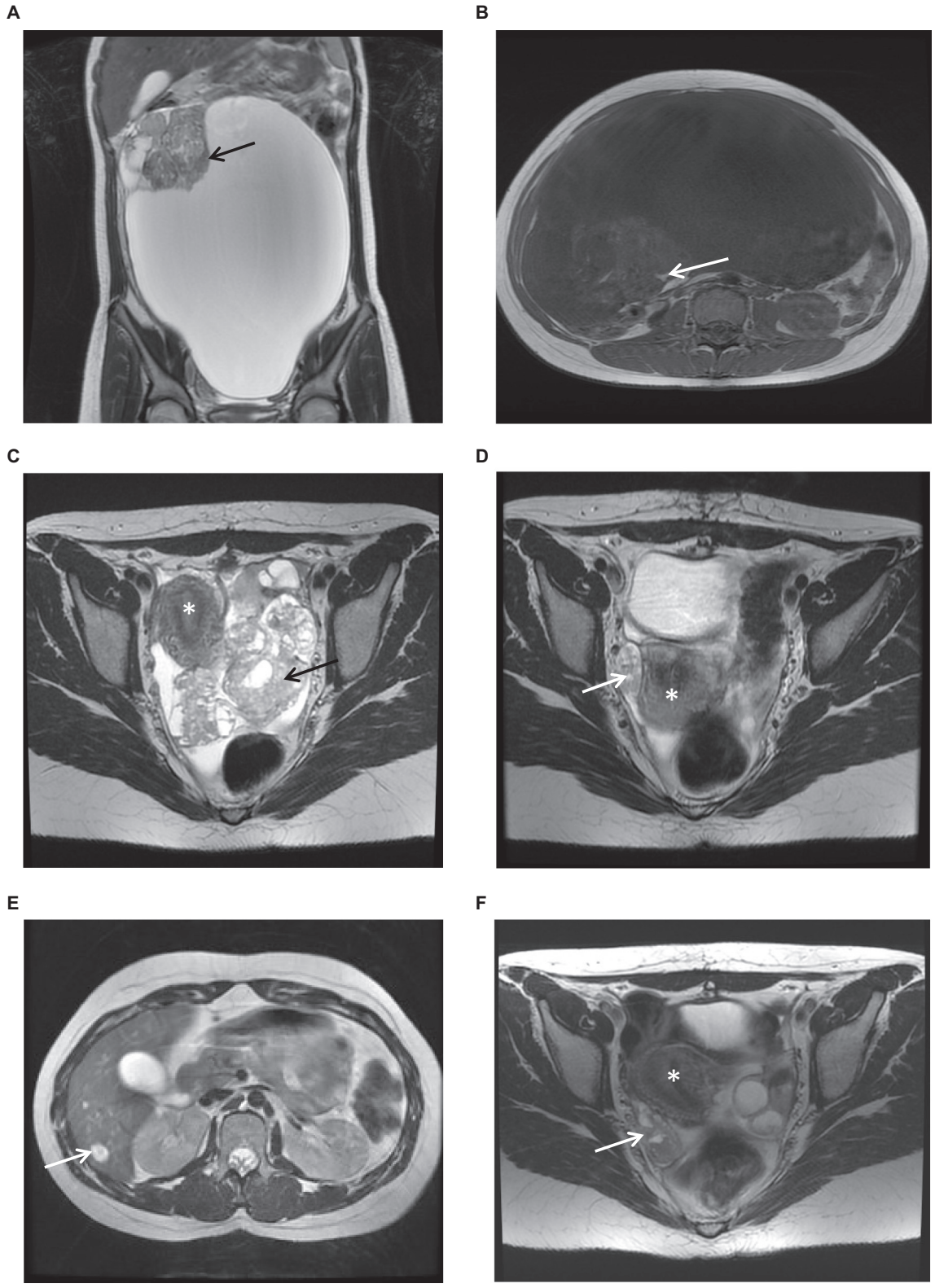

Fig. 2. Radiological imaging for the ovarian immature teratoma case. A) Coronal T2 weighted MR image at diagnosis demonstrating a large cystic lesion arising from the right ovary occupying the entire abdomen and pelvis with complex solid contents (arrow); B) axial T1 weighted MR image demonstrating areas of high signal intensity (arrow) in keeping with small areas of fat; C) axial T2 weighted MR image five months following right salpingo-oophorectomy showing a complex mass (arrow) posterior to the uterus (*) consistent with first recurrent disease; D) axial T2 weighted MR image two months following surgical resection of pelvic recurrence demonstrating a complex mass in the right adnexa (arrow) adjacent to the uterus (*) in keeping with second recurrent disease; E) axial T2 weighted MR image at the same examination as in D) demonstrating a new liver lesion (arrow) confirming metastatic disease; and F) Axial T2 weighted MR image of the pelvis following two cycles of chemotherapy revealing an increase in size of the lesion (arrow) posterior to the uterus (*).

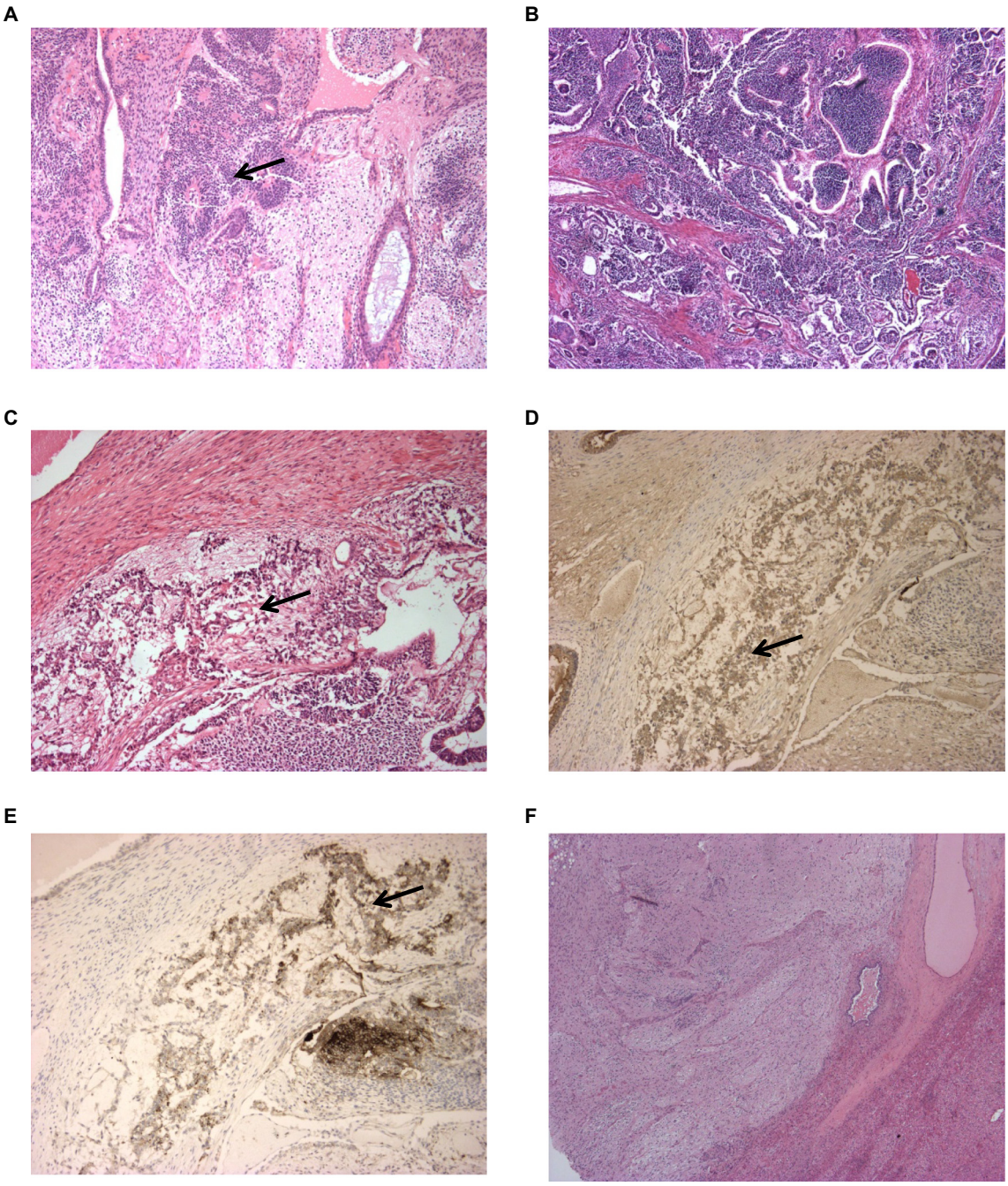

Fig. 3. Histopathologic appearances of the resection specimens. A) Primary ovarian resection specimen showing focus of immature neuroepithelium (arrow) with surrounding mature elements (×40); B) resection specimen from first recurrence showing extensive immature neuroepithelium throughout image (×40); C) 'microfoci' of yolk sac tumor (arrow) at first recurrence (×400); D) and E) AFP and glypican-3 staining (arrows), respectively, of the same focus as in C) (×400); and F) hepatic resection specimen of second recurrence post-chemotherapy, showing deposit of mature teratoma (left) with native liver present (right) (×40).

and may be pigmented; mitoses may be abundant [1,2]. There is often also immature mesenchyme in the form of loose, myxoid stroma; immature osteoid, rhabdomyoblasts, fat and cartilage may also be seen. Less commonly, immature endodermal structures may additionally be observed. Regarding molecular characteristics, 90% of IT tumors classified as grade 1–2 are diploid, whilst 66% of grade 3 (high-grade) tumors are aneuploid [2]. Moreover, karyotypic abnormalities are most commonly seen in grade 3 (high-grade) IT [2]; this biologic phenomenon may account for the increased propensity of grade 3 disease to recur in both pediatric and adult populations [6] (see also Section 7 below). Overall, ovarian IT shows fewer DNA copy number changes compared with other ovarian malignant GCTs [2]. Unfortunately, there is a paucity of published information on additional molecular characteristics of IT. Particular areas of unmet clinical need include using biological changes to identify which patients are destined to relapse and identifying the genes/pathways involved in IT pathogenesis that may be amenable to the testing of novel agents. Of note, there is some limited evidence that CDK4/6 activation may contribute to the development of *mature* teratoma (MT), and hence there are some reports of neoadjuvant use of CDK4/6 inhibitors such as palbociclib in MT where upfront surgery is deemed not feasible [17,18], but this is not indicated for IT. Further molecular study of IT is therefore required to improve our understanding of this rare disease and facilitate clinical management.

5. Classification system

Originally, IT was classified using the Norris Grading System into grades 1 to 3, based on the quantity of the immature neuroepithelial component they contained [1]. Grade 1 was defined as a tumor with rare foci of immature neuroepithelial tissue which occupy <1 low power field (LPF) (40× objective) in any slide. Grade 2 was as for grade 1 but with immature elements occupying 1 to 3 LPFs (40× objective) in any slide. Grade 3 was defined as a tumor with a large amount of neuroepithelial tissue occupying >3 LPFs (40× objective) in any slide. In the 2014 WHO publication, it was suggested that a grading system which divided IT into two tiers (low-grade and high-grade) could more commonly be used [2]. As a result, those that were previously grade 1 are now considered low-grade and previous grades 2 and 3 are now considered high-grade. It should be noted that the 2014 WHO publication still quotes both classification systems and provides criteria for grade 3 IT disease [2].

6. Surgical staging and ovarian preservation

From a surgical perspective, patients presenting with an ovarian mass undergo a pre-operative assessment with imaging (typically USS and MRI) and serum tumor marker estimation [19,20]. There has been a gradual move by pediatric surgeons to adopt fertility preserving approaches where possible [19–21], i.e. electing to perform an ovarian cystectomy rather than oophorectomy where pre-operative imaging and tumor markers suggest a likely non-malignant diagnosis. In this case however, the MRI features suggested IT and importantly did not identify any normal right-sided ovarian tissue. Consequently, and taken in conjunction with the pre-operative raised AFP, the decision was made during surgery itself to perform an oophorectomy rather than cystectomy, in case these findings were indicative of malignant GCT disease. At surgery, the whole peritoneal cavity is inspected, ideally by laparoscopy, washings are obtained, biopsies are taken of any additional lesions and ideally, the primary lesion is removed cleanly and *en bloc* without rupture, if feasible. In this case, due to gross tumor size (Fig. 2A/B), surgical aspiration was necessary first to facilitate resection.

For low-grade IT where oophorectomy is required, removing only the affected ovary and fallopian tube (and hence preserving the contralateral ovary, tube and uterus and thereby fertility), is sufficient and does not increase chances of recurrence [21,22]. The rationale for removing the tube with the affected ovary is that this reduces subsequent ectopic tubal pregnancy risk. Given that IT generally presents in young women, maintenance of fertility where possible is important in this patient group. Fortunately, studies have shown that where fertility-sparing surgery is used, reproductive outcomes are favorable in that up to 80% of patients attempting to conceive become pregnant [21,23–25].

7. The role of adjuvant chemotherapy for ovarian immature teratoma

There is ongoing controversy surrounding the role of adjuvant chemotherapy in IT following surgery. Chemotherapy has almost universally been delivered to adult patients [6,26], with the standard-of-care in gynecologic oncology practice being chemotherapy for all women with ovarian IT, except for FIGO stage IA, grade 1 disease [6]. However, because there is no evidence that chemotherapy is of benefit in children, pediatric patients with IT are usually treated with fertility-preserving surgery alone, with similar excellent outcomes [5]. In 2016, the Malignant Germ Cell International Consortium (MaGIC; https://www.magicconsortium.com/) reviewed a large series of both pediatric and adult IT cases to determine the role of chemotherapy in management of IT [6]. They merged data from seven pediatric and two adult trials to comprise a data set of 179 patients (98 pediatric; 81 adult). There was no evidence that administration of adjuvant chemotherapy at first presentation (i.e. following diagnosis obtained through surgery) decreased recurrences/events in the small number of cases within the pediatric cohort who were treated this way (eight of 98 cases) [6]. The 5-year event-free survival (EFS) and overall survival (OS) was 91% and 99%, respectively, for the pediatric cohort and 87% and 93%, respectively, for the adult cases. Among grade 3 pediatric patients, the 5-year EFS was 92% for stage I/II but significantly lower for the stage III cohort at 52% ($p = 0.005$) [6]. Similar outcomes were seen in adult patients with grade 3 disease, with 5-year EFS of 91% for stage I/II disease but 65% for stage III/IV cases ($p = 0.01$) [6].

Confirmation of the wider applicability of this approach, i.e. avoiding adjuvant chemotherapy after surgery for IT, came from a recent report describing ovarian IT in adult patients [27]. Newton et al. studied 138 patients across four large UK cancer centres over 12 years; EFS was 72% and OS 93% [27]. They showed that adjuvant chemotherapy did not reduce future relapse or progression in IT patients and they observed no radiologic responses to chemotherapy in IT. The authors concluded that IT is chemotherapy resistant and suggested exclusive surgical management of ovarian IT in patients of all ages [27]. To assess this conclusion prospectively, the current AGCT1531 trial (ClinicalTrials.gov identifier: NCT03067181) enrolls pediatric and adult patients (aged 0–50 y) with stage I ovarian IT disease (both FIGO IA and IB), regardless of grade, to a 'watch and wait' surveillance strategy and if confirmed to be successful, this could be extended to higher stages of disease.

However, optimal management at the time of IT relapse remains open to debate [6], and is due to the paucity of published information in such cases. This lack of data is multifactorial, including the rarity of the disease, the multiplicity of clinicians looking after such patients, and the difficulty of distinguishing between a recurrence of IT from, for example, gliomatosis peritonei or 'growing teratoma syndrome' (GTS), where AFP levels are, by definition, normal in both latter scenarios [14]. Those who argue that IT is purely a surgical disease do so because IT is already predominantly differentiated and therefore does not remain sufficiently undifferentiated to be able to respond to chemotherapy [5,27].

8. Growing teratoma syndrome following chemotherapy

A further issue to consider in the use of adjuvant chemotherapy where residual or recurrent IT disease exists is the potential to cause GTS. GTS is the phenomenon of growth of the tumor mass during or shortly after chemotherapy in association with normalized tumor markers, e.g. AFP [28–31]. GTS has been reported to occur in 12% of ovarian GCTs, most commonly in the retroperitoneum [32–34]. GTS can occur in patients with IT or with mixed malignant GCTs who receive chemotherapy. Due to the low number of reported cases, the mechanism of GTS formation is unclear, but two hypotheses exist. The first and most plausible explanation is that chemotherapy transforms and differentiates more 'malignant' GCT cells into larger and more 'benign' teratomatous cells. The second is that the chemotherapy can only destroy malignant cells, and so it leaves chemoresistant teratoma behind [34], although this explanation does not necessarily fully explain why such lesions become larger. It is important to note that even if a patient is not exposed to chemotherapy, IT has the potential to convert into mature disease if post-surgical recurrence occurs [10].

9. Rationale for carefully selected use of adjuvant chemotherapy in index case

In our case, at first recurrence there was debate as to whether the histologic findings represented high-grade IT with YST microfoci or a mixed malignant GCT, in view of the observation that some foci of YST within the lesion were edging beyond the criteria for a microfocus. In

view of the macroscopic complete resection at surgery, and combined with the knowledge of the declining AFP post-operatively, it was decided to follow a close surveillance strategy. A strong rationale for not giving adjuvant chemotherapy in this setting was the lack of biochemical (AFP) and radiologic evidence of disease to monitor the effectiveness or otherwise of such therapy. A second recurrence occurred shortly afterwards, heralded by a modest rise in AFP, with adnexal disease and a metastatic hepatic lesion, and consequently, a joint decision was made to initiate chemotherapy at this stage, given the history of two previous surgeries that had not prevented further relapse. It should be noted that these lesions were not biopsied prior to chemotherapy, and therefore whether they represented high-grade IT with YST microfoci or a true mixed malignant GCT at this timepoint remains open to debate. That notwithstanding, with chemotherapy the lesions increased in size, due to maturation of the lesions consistent with GTS, and so chemotherapy was discontinued and surgery performed. Disease volume therefore needs to be factored into MDT discussions when considering the use of chemotherapy. If large volume disease and/or compression of vital abdominal-pelvic organs and structures is present, then surgical resection needs to be undertaken prior to consideration of chemotherapy, which may well result in GTS in this setting and exacerbate pre-existing symptoms. Here, post-operative histology showed that the lesion posterior to the uterus was down-graded from high-grade to low-grade IT and the anterior uterine and liver lesion had differentiated into MT. When treating IT in such carefully selected cases with chemotherapy, an increase in the size of tumors can be expected, but we postulate that in this patient the success in differentiating most of the disease from IT to MT and down-grading of high-grade IT to low-grade disease altered the natural history of the disease process and prevented further recurrences. The patient is now 18 months following second event. Hence, we suggest chemotherapy could be reserved for patients, regardless of age, who experience a second or subsequent early recurrence of IT following surgery, with guidance from serum AFP levels (if informative at original diagnosis) correlated with radiologic and histologic findings. This approach may also minimize the post-surgical morbidity from repeated surgical interventions, such as bowel adhesions.

10. Surveillance recommendations

In pediatric oncology practice, post-operatively ovarian IT patients in the United Kingdom are generally followed-up with USS and AFP measurement at three monthly intervals (once normalized) for three years as per the Children's Cancer and Leukaemia Group (CCLG) guidelines (https://www.cclg.org.uk/). If they develop symptoms but are found to have an apparently normal USS, 3D imaging (MRI or CT) is performed. USS surveillance is an excellent tool which has a high accuracy and sensitivity particularly when performed by specialized radiologists. It also has the advantage of no radiation, no injection of intravenous contrast medium or necessity to lie still on a gantry table for sustained periods. Unfortunately, USS has limitations in that it may not detect small peritoneal gliomatosis deposits and subtle lesions can be obscured by bowel gas. MRI and CT are both excellent at demonstrating peritoneal gliomatosis and more focal areas suspicious for recurrent disease. In addition, if there are suspicious findings on USS these techniques will be used to assess the extent of recurrent disease and the accessibility of sites for possible surgery. For patients where there is known residual disease, CT and MRI are used for surveillance as it can be difficult to distinguish subtle changes in disease response on USS. However, in pediatric practice it should be noted that the importance of routine CT or MRI follow-up is reduced as surgery is not instigated unless the gliomatosis is symptomatic — USS and AFP estimation are performed instead and patients typically only proceed to 3D imaging if symptomatic and USS has not demonstrated any lesions.

11. Summary

Patients with ovarian IT are rare and recurrences are uncommon. Historically, adult and pediatric patients with this disease have been managed very differently. Adult patients have routinely been managed with adjuvant chemotherapy, and pediatric patients merely with post-operative surveillance, but both with excellent outcomes. We report a 12-year-old girl with ovarian IT who experienced two early recurrences after surgery, following which chemotherapy was initiated that resulted in enlargement of the lesions due to GTS, as expected, but which matured the lesions predominantly to MT. Eighteen months into follow-up, the patient remains well and disease-free. The rarity of such cases highlights the need for multidisciplinary and wider discussion to ensure optimal patient outcomes. In the absence of a strong biologic rationale to the contrary, we suggest most patients, regardless of age, could undergo surveillance only, with chemotherapy reserved for very carefully selected cases, aiming to alter the natural history of the disease.

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Author contributions

JLF and MJM devised the original idea for the case report as a Tumor Board article, derived clinicopathologic data from the medical notes, produced the serial AFP figure (Fig. 1) and wrote the manuscript. CEH provided the histologic images (Fig. 3) and co-wrote the manuscript. HCA provided the radiologic images (Fig. 2) and co-wrote the manuscript. CRJ and JL undertook surgery on the patient and co-wrote the manuscript. JCN was the patient's primary physician and co-wrote the manuscript.

Declaration of Competing Interest

None.

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