Excision of extensive metastatic dysgerminoma to control refractory hypercalcaemia in a child at high risk for tumour-lysis syndrome

Wajid Jawaida, Valeria Solarib, Lisa Howellic, Edwin Jesudasond,*

aDivision of Child Health, University of Liverpool, Liverpool L12 2AP, UK
bSchool of Biological Sciences, University of Liverpool, Liverpool L69 7ZB, UK
cAlder Hey Children’s Hospital, Liverpool L12 2AP, UK
dAlder Hey Children’s Hospital and University of Liverpool, Liverpool L12 2AP, UK

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Abstract Hypercalcaemia is a rare life-threatening complication of paediatric cancer that is commoner in haematological than solid malignancies and associated rarely with acute renal failure. Often refractory to medical therapy, control of hypercalcaemia in children with solid tumours may necessitate excision of localised tumours or urgent chemotherapy for metastatic ones. We present a child with refractory hypercalcaemia, bulky chemosensitive metastatic tumours and acute renal failure in whom chemotherapy posed high-risk of tumour lysis syndrome (TLS). Resection of the metastatic tumours successfully normalised the hypercalcaemia and represents a practical alternative control strategy in cases at high risk of TLS.

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Compared to adults, malignant hypercalcaemia in children with cancer is uncommon; however, it may still be associated with life-threatening consequences [1]. Most cases are associated with haematological malignancies and are treated medicinally. In children with solid tumours, malignant hypercalcaemia is rarer still and may be highly resistant to medical treatment (resolving only once the tumour is excised) [2]. Dysgerminomas are classic examples where excision of isolated ovarian lesions has promptly controlled associated hypercalcaemia [2,3]. In children with huge ovarian primaries judged unsuitable for primary excision, chemotherapy and even tumour chemomobilisation have been tried instead for calcium control [4]. Frankly metastatic dysgerminoma with severe hypercalcaemia is rarer still; in addition to standard medical therapy for hypercalcaemia, oncological strategies to control tumour-led hypercalcaemia in adults (≥16 years) have included radiotherapy, chemotherapy and even bilateral salpingo-oophorectomy (with and without total abdominal hysterectomy) [5-8]. In contrast, metastatic dysgerminoma with severe hypercalcaemia is extremely rare in prepubescent girls. In one such case, where renal function was reasonable, control of hypercalcaemia was
achieved with pamidronate and calcitonin (allowing chemotherapy and surgery for definitive oncological therapy) [9]. We report a highly unusual case of a prepubescent girl with extensive retroperitoneal, utero-ovarian and pelvic tumours, who presented with hypercalcaemia (>3.75 mmol/l) and renal failure (creatinine >360 mmol/l). Her hypercalcaemia proved resistant to medical therapy and the decision was taken to carry out surgical excision to control the hypercalcaemia, obtain a tissue diagnosis and avoid the high risks of chemotherapy-induced tumour lysis syndrome (attendant upon tumour bulk, high chemosensitivity and renal failure) [10,11].

1. The case

This karyotypically-normal female presented at 10 years of age with a 2 week history of pallor, lethargy and subacute abdominal symptoms and was noted on initial assessment to have a large abdominal mass. The admitting medical and surgical teams arranged an abdominopelvic CT scan; contrast was withheld due to her hypercalcaemia and renal dysfunction. The scans revealed three large masses (Fig. 1): the first para-aortic mass extended from the liver to the ipsilateral common iliac vessels; the second, lying more anteriorly across the lower abdomen,

![Preoperative CT scan taken without contrast due to renal failure.](image)

Fig. 1 Preoperative CT scan taken without contrast due to renal failure. A - Coronal view showing the retroperitoneal mass (horizontal arrow) and pelvic mass (oblique arrow) and relations to the aortic bifurcation; B - Coronal view showing the retroperitoneal mass (horizontal arrow) and ovarian lesion (vertical arrow); Transverse views showing (arrowed) the retroperitoneal mass and associated hydronephrosis (C), the ovarian mass (D) and pelvic mass (E).
exhibited variegated calcification; the third mass was in the right side of the pelvis below the common iliac vessels. Given the calcification on imaging, the hypercalcaemia and a mildly elevated $\beta$-hCG, a provisional diagnosis of metastatic ovarian dysgerminoma was made. There was no evidence of bony metastases or changes such as abnormal PTH-like peptides or Vit D levels. The renal impairment was attributed to the severe hypercalcaemia.

**Fig. 2** Intraoperative photographs. These pictures illustrate the limitations of non-contrast CT for identifying vascular anatomy. MRI may have been a preferable in this instance. A - The right retroperitoneal mass (arrows) with the renal veins and inferior vena cava (IVC; dotted lines) chronically effaced over the surface; B – Omental covered right ovarian mass (horizontal arrow) extending to and filling the uterus (external margin demonstrated by oblique arrows); C – Superior pole of pelvic mass (horizontal arrow) lying between right internal iliac (not seen) and right external iliac (vertical arrows) arteries with adjacent right ureter (oblique arrow) crossing the ipsilateral common iliac vessels. D – IVC, right renal vein and renal artery (vertical arrows), right kidney (horizontal arrow) and ipsilateral ureter (oblique arrows) after excision of the retroperitoneal mass. Preoperative scans had not shown that the mass displaced arterial structures posteriorly and the venous ones anteriorly; E – tumour-involved uterus opened out along its right hand margin with the edges arrowed. This involvement was not predicted on the scans. The uterus was repaired and retained in a fertility-sparing approach; F – Right obturator nerve (vertical arrows) and external iliac artery (horizontal arrow) seen after pelvic mass excision.
Medical treatment for hypercalcaemia (including hydration and bisphosphonate therapy) was attempted over the next few days without success. Further options to control the hypercalcaemia were considered at the oncology multidisciplinary meeting (see discussion). Having reviewed the CT scans, the consensus was to pursue surgical excision as a method to secure normocalcaemia, stabilise renal function and minimize risks of tumour lysis.

2. The surgery

Laparotomy revealed the three masses seen on scans (Fig. 2): the first displaced the supra- and infrarenal cava anteriorly and was 'pegged' in place bilaterally by the renal and iliac veins. The arterial network lay behind this mass beyond immediate visualization. A second mass was covered with adherent omentum and featured a large draining vein that joined the cava in such a way as to indicate that this mass, at least in part, was the right ovary. Contiguous with this was the uterus whose wall was invaded by tumour from the right side and which was full of tumour too. A third mass lay in the right side of the pelvis between the ipsilateral internal and external iliac vessels. No evidence of peritoneal deposits was found.

In view of the need to control the malignant hypercalcaemia, we aimed to excise all three masses (Fig. 2) without jeopardizing other organs. We mobilized and controlled each of the overlying major veins sufficiently to allow the upper mass to be excised en bloc. Once the aorta was cleared, the right renal artery was freed from the posterior surface of the tumour (which extended between the right renal artery and vein to the level of the adrenal gland). The right ovarian lesion was excised along with the omentum. Since this second mass invaded along the ipsilateral tube into the uterus, the tumour was shaved off the uterus. The tubal insertion and side of the uterus were also opened to allow luminal tumour to be debulked prior to uterine closure. The third mass was excised from between the right internal and external iliac vessels after freeing off and preserving the overlying obturator nerve. Hence the completed tumour resection comprised all of the retrocaval, pelvic and ovarian tumours, the ipsilateral Fallopian tube, the omentum, perirenal fat and peri-renal, pelvic and para-aortic nodes; no other normal tissue was removed (so the contralateral tube and ovary remain intact). Tumour was found throughout the principal three masses (retroperitoneal, pelvic and tubo-ovarian) as well deposits in the omentum and one suprarenal node. Histology from these sites showed dysgerminoma without evidence of germ cell line differentiation and featuring lobules of large polygonal tumour cells with eosinophilic cytoplasm of finely vacuolated/granular appearance and round/oval medium sized nuclei.

Postoperative recovery was unremarkable except for temporary hypertension (controlled briefly with medication). Renal doppler ultrasound showed no problems with postoperative renal perfusion. Renal function has improved postoperatively without any need for dialysis, but it has failed to normalize completely (serum creatinine (normal range, 36 - 69 mmol/l) = 85 mmol/l at 11 months postoperatively).

Fig. 3  Graph showing levels of calcium, creatinine and total HCG against time. The date of surgery (day 0) and periods of chemotherapy are marked. Postoperatively, and before chemotherapy, calcium and HCG normalize, consistent with the ≥99% gross total excision of metastatic disease (limited only by uterine sparing). Renal function as indicated by serum creatinine improves but does not normalise.
Excision of dysgerminoma to control hypercalcaemia

From the preoperative peak calcium of 3.77 mmol/l (normal range uncorrected = 2.15-2.74 mmol/l), hypercalcaemia successfully resolved following resection and prior to chemotherapy (Fig. 3). Similarly, total HCG (normal range = 0 – 10 miu/ml) fell from a preoperative high of 194 miu/ml to normal levels (4.3 miu/ml) by day 12 post-operatively (prior to chemotherapy) and remains <1.0 miu/ml at 11 months post-surgery and 8 months post-chemotherapy (AFP was elevated neither pre-nor postoperatively). Post-operative chemotherapy was scheduled as shown in Fig. 3 and comprised 4 cycles of etoposide, vincristine and carboplatinum, (calculated for an area under the curve of 7.9 mg/ml/min, using the Newall formula and t1/2 on EDTA Glomerular Filtration Rate measurement). Postoperative MR scans have confirmed clearance of the retrocaeval, pelvic and ovarian masses with a grossly normal looking uterus (Fig. 4). Almost a year later, scans, tumour markers and serum biochemistry have revealed no evidence of recurrent tumour or hypercalcaemia.

3. Discussion

Malignant hypercalcaemia in children with solid tumours is rare [1]. However the surgical oncologist can help treat hypercalcaemia by resecting the responsible tumour(s) when available medical therapies have failed and / or associated factors such as renal dysfunction increases their risks.

Previous reports have described removal of isolated ovarian dysgerminomas to control malignant hypercalcaemia in children [2,3]. Rare cases of hypercalcaemia in adults with metastatic dysgerminoma have been managed in a variety ways, ranging from abdominal radiotherapy or chemotherapy to bilateral oophorectomy, with or without hysterectomy [5-8]. In one child with hypercalcaemia, metastatic dysgerminoma and relatively preserved renal function, palmidronate and calcitonin sufficed for calcium control [9]. In our case, the child was in renal failure with bisphosphonate therapy having proved ineffective.

We therefore considered the options reported in adults with metastatic dysgerminoma and refractory hypercalcaemia. Abdominal radiotherapy was discounted due to its substantial short- and long-term side effects. Chemotherapy after biopsy would have been our standard procedure for bulky, locally metastatic dysgerminoma in the absence of hypercalcaemic renal failure. In this case, however, the need to control serum calcium and deal with the acute renal failure prompted careful reconsideration of leading with chemotherapy. First, there was concern that chemotherapy might be ineffective given reports suggesting tumour excision can be necessary (and rarely still not sufficient) for hypercalcaemia control [2,12]. Second, and perhaps most importantly, the anti-tumour effects of chemotherapy and its side effects are non-trivial in the context of a child in hypercalcaemic renal failure. Aside from the nephrotoxic effects of chemotherapy itself (in particular platinum use for dysgerminoma), tumour lysis syndrome (TLS) in solid tumours has been estimated to have a 36% mortality rate with clear risk factors, many of which were present in this case (bulky disease (>10 cm), pre-existing renal failure, raised uric acid, concurrent nephrotoxins, involvement of abdominal organs, high tumour sensitivity to cytoreductive agents) [10]. Recent international guidelines classify TLS risk into low, intermediate and high-risk groups. Our case classifies as high risk (>5%) of tumour lysis syndrome due to bulky disease, highly chemosensitive tumour and renal failure. Pursuing the chemotherapy option would also have required general anaesthetics for both biopsy and subsequent post-chemotherapy resection (assuming chemotherapy failure did not necessitate earlier surgery). Chemotherapy has also been reported to make subsequent excision of retroperitoneal dysgerminoma more difficult in adults [13]. Since dysgerminomas produce humoral factors to drive hypercalcaemia, excision of even metastatic disease remains a rational strategy to control this [6,14]. Takemori et al described the massive para-aortic disease that can accompany dysgerminoma (albeit without hypercalcaemia in that case) [15]. Our CT scans indicated, that though large, the three masses were localized and not particularly infiltrative in appearance. This suggested primary excision of metastatic disease was feasible, albeit with some uncertainty about the vascular anatomy (due to the lack of iv contrast); furthermore, the extent of uterine involvement was also unclear from the imaging. In this regard, an MRI may have been more helpful than the CT scan arranged on admission. Seeking further guidance from the literature, we were unable to find any similar reported cases where surgical excision of...
metastatic disease was used to control refractory hypercalcaemia in young children; although, a few adult cases had reported using bilateral oophorectomy and even hysterectomy, we sought to avoid this.

Surgery in the present case provided secure control of the malignant hypercalcaemia without significant surgical morbidity or further nephrotoxic insult. Retroperitoneal dissections for metastatic germ cell tumours are well described, but most now follow chemotherapy rather than precede it. In common with several other paediatric tumours, it is plausible in this case that resection was facilitated by the absence of chemotherapy-induced fibrosis but hampered by the persisting tumour size and vascularity. The latter is of practical consequence since sizeable lesions with vessel encaement, or with entrapment beneath major vasculature, may benefit less than sizeable lesions with vessel encasement, or with entrapment beneath major vasculature, may benefit less.

Although complete excision of isolated primary dysgerminomas can control malignant hypercalcaemia, the literature provided little guidance as to whether debulking or complete resection of metastatic disease is required. We undertook a complete macroscopic clearance of both retrocaval and pelvic tumours. Since the ovarian lesion (and presumed primary) was invading the uterus, we balanced the need to control hypercalcaemia with that of preserving the uterus. Although the normal uterine appearances on postoperative scans provide grounds for optimism, it remains to be seen whether normal uterine function will emerge after such extensive tumour involvement. In the event, uterine-sparing resection did not compromise control of hypercalcaemia despite the minimal residual uterine disease that it entailed: we would therefore emphasise that hysterectomy, (as described in a young adult case with presumed metastatic disease) or indeed the sacrifice of other major structures need not form part of surgical control of refractory hypercalcaemia in children.

Although post-operative serum urea and creatinine were improved compared to pre-operative levels, renal function has not completely normalized even several months after surgery and subsequent chemotherapy. Whilst it is possible that the hypercalcaemia alone was responsible for this lasting impairment, a multifactorial aetiology seems plausible, with chronic tumour compression of the renal veins and cava another potential contributory factor. Moreover, other renal disorders have been associated with dysgerminoma [9,17]. Currently a genetics opinion is being sought to look for a possible syndrome linking the 2 entities.

In summary, resection of large metastatic dysgerminomas can successfully control malignant hypercalcaemia that is refractory to medical therapies. Surgery therefore may be a useful option for children in hypercalcaemic renal failure with additional strong risk factors for chemotherapy-induced tumour lysis syndrome. Excision of such tumours requires attention to effaced overlying major veins and should not prejudice key organs such as the uterus. Debunking and preserving the tumour-invaded uterus, we nevertheless performed a >99% gross total excision as illustrated by prompt normalization of total HCG prior to chemotherapy: minimal residual disease in the spared uterus does not appear to forfeit hypercalcaemia control.

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