Case Report

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Immature ovarian teratoma with gliomatosis peritonei, paraneoplastic hyponatremia and growing teratoma syndrome: a case report and literature review

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Introduction and relevance: Paraneoplastic hyponatremia is often secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) by tumour cells. Immature ovarian teratomas (IOT) are uncommon and may present with SIADH.

Case report: A 26-year-old female presented with a 3-month history of abdominal pain and constipation. Imaging identified a mixed solid-cystic right ovarian mass containing fat and peritoneal deposits. Biochemistry showed severe, refractory hyponatremia (117 mmol/l). She underwent diagnostic fertility-preserving right salpingo-oophorectomy and resection of peritoneal nodules with the aim to achieve symptom control and hyponatraemia resolution. Pathology revealed a FIGO Stage 2 Grade 2 IOT with extensive benign peritoneal gliomatosis. Initial management was conservative. After 6 months of active follow-up, a rise in AFP, and recurrent hyponatremia supported the decision to administer three cycles of Bleomycin-Etoposide-Cisplatin chemotherapy. One month later, given radiological disease progression despite satisfactory biomarker response, cytoreductive surgery with complete macroscopic resection was performed. Pathology consisted solely of peritoneal mature glial elements: a growing teratoma syndrome (GTS). The patient remains disease-free after 2 years of surveillance.

Clinical discussion: Specimen histological assessment from the patient's initial surgery showed immature neuroectodermal tubules, which are thought to be the source of vasopressin secretion. The authors hypothesise that recurrent hyponatremia and rising AFP levels represented postoperative disease relapse. Biochemical response despite radiological disease progression was pathognomonic of a GTS.

Conclusion: Paraneoplastic SIADH secondary to an IOT must be considered in female patients presenting with abdominal symptoms and hyponatremia. Management requires a multidisciplinary approach. Serum electrolytes are useful surveillance biomarkers supplementary to tumour markers.

Keywords: case report, gliomatosis peritonei, growing teratoma syndrome, hyponatremia, immature ovarian teratoma, syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

HIGHLIGHTS

- Immature ovarian teratoma (IOT) is a rare ovarian tumour occurring mostly in women of reproductive age.
- IOT should be included in the differential diagnosis for women with abdominal distension and hyponatremia refractory to medical treatment.
- IOT may be associated with gliomatosis peritonei (GP), which consists of peritoneal mature glial implants.
- Growing teratoma syndrome is a rare outcome after surgery and/or chemotherapy for immature ovarian teratoma, where residual mature elements grow following treatment despite normalised tumour markers.
- Paraneoplastic (euvolaemic) hyponatremia with IOT is secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) and can result in neurologic symptoms. SIADH-related hyponatraemia can be refractory to medical treatment, and surgery remains the gold-standard approach to resolve it.

Introduction

Immature ovarian teratomas (IOT) are rare malignant ovarian germ cell tumours (GCT), constituting less than 1% of ovarian teratomas, typically occurring in the first two decades of life[1,2]. Managing ovarian pathology in this age group is particularly

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complex because it can have lasting effects on fertility, leading to both emotional and financial burdens for the patient and her family.

IOTs are predominantly unilateral, composed of mature tissue from various lineages and an immature neuroepithelial cell component[3]. Their prognostic profile is determined by the histologic grade, which is based on the amount and degree of cellular immaturity of the neuroepithelium. Grade 1 tumours hold a 95% survival rate, while grades 2–3 exhibit an increased risk of recurrence and lower overall 5-year survival (85%)[4]. For premenopausal women, unilateral salpingo-oophorectomy and surgical staging is recommended[1,4]. Post-surgery, surveillance in the form of ongoing surgical follow-up suffices for Stage I Grade 1 tumours, while chemotherapy is reserved for Stage I Grade 2–3 and ≥ Stage II tumours[1,2,5].

Gliomatosis peritonei (GP) is a rare condition often coexisting with IOT, and features mature glial deposits in the peritoneum[6,7]. Mature GP elements are associated with a favourable prognosis, although malignant transformation has been reported[8,9].

Residual or progressive disease post-surgery and/or chemotherapy, with normalised tumour markers, may indicate residual mature teratoma elements, constituting a growing teratoma syndrome (GTS)[2,5]. GTS, refractory to both chemotherapy and radiotherapy, exhibits an excellent prognosis if complete resection is achieved[2,4,5].

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a well-documented paraneoplastic syndrome that causes hyponatremia due to ectopic vasopressin production by malignancies[10,11]. It has been mainly reported in small-cell lung carcinoma but also in a few cases of IOT[11–17].

This report details a case of IOT with GP and hyponatremia due to paraneoplastic SIADH, with GTS development post-surgery and chemotherapy. This case report has been reported in line with the SCARE Criteria[18].

Case report

Patient information

A 26-year-old nulliparous female presented to the emergency department with a 3-day history of altered bowel habit, abdominal pain, and dizziness. Prior to this, she had been experiencing abdominal distension, early satiety, nausea, and severe constipation with excessive laxative use for three months. She had no notable family history of gynaecological cancers, medical or surgical history, did not smoke or consume alcohol, had irregular menstrual cycles and was not on any form of contraception. Her Eastern Cooperative Oncology Group performance status was 0.

Clinical findings

The patient's BMI was 23. Upon examination vital signs were normal. Neurologic examination revealed a positive Romberg test indicative of proprioceptive dysfunction. A palpable mass measuring 20 cm, up to the level of the umbilicus was noted, without shifting dullness or fluid thrill. She had no clinical signs of fluid overload or oedema.

Diagnostic assessment and interpretation

Pelvic MRI and computed tomography of the chest, abdomen, and pelvis (CT-CAP) revealed a 21.5 cm right ovarian mass containing fat and calcification. There was gross ascites and plaques of peritoneal disease in the pelvis, encasing the recto-sigmoid, extending to the omentum, paracolic gutters, and bilateral diaphragms. Chest and head imaging were normal. Following these findings, serum tumour marker testing was performed, including markers that are typically raised in germ cell or sex-cord tumours that are more prevalent in younger age groups (HCG, AFP, LDH)[5]. Biochemical testing revealed elevated CA-125 (338 kunits/l), CA19-9 (230 units/l), and alpha-fetoprotein (100 kunits/l), with normal CEA (8.2 units/l), LDH (207 units/l), and HCG (< 1 units/l) levels. This tumour marker profile was in keeping with a suspected diagnosis of immature ovarian teratoma. Differential diagnoses included epithelial ovarian cancer subtypes and other germ cell tumours such as yolk sac tumour. The patient's case was discussed at the gynaecologic oncology multidisciplinary meeting, leading to the recommendation of an emergency laparotomy for unilateral salpingo-oophorectomy, omentectomy and peritoneal biopsies.

Preoperative blood tests revealed severe hyponatremia (117 mmol/l), decreased from 128 mmol/l one month earlier. Thyroid function tests, albumin, and cortisol levels were normal. Urinary sodium was 52 mmol/l, serum osmolality was low (240 mmol/kg) and urine osmolality was normal (245 mmol/kg). Endocrine evaluation suggested a paraneoplastic origin for the hyponatremia, exacerbated by laxative use.

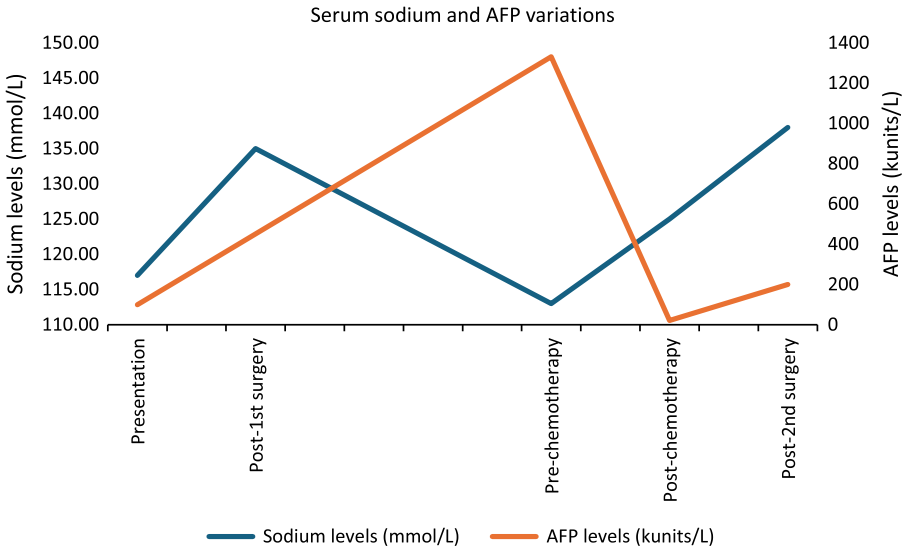
Therapeutic intervention

Hyponatremia was gradually corrected to reduce anaesthetic risk. Electrolyte management involved strict fluid restriction (250 ml/day) and hypertonic saline bolus infusions. Surgery, performed by a consultant-led surgical gynae-oncology team took place three days later at a sodium level of 127 mmol/l. The procedure included a midline laparotomy, right salpingo-oophorectomy, omental and peritoneal biopsies. Intra-operatively, a 22 cm right ovarian cyst, 1-l ascites, and widespread abdominal and pelvic peritoneal disease were seen, in keeping with FIGO 3C surgical staging. Postoperative sodium levels normalised (135 mmol/l), and the patient was discharged six days post-surgery.

Follow-up and outcomes

Histopathological examination identified a stage 2 grade 2 immature ovarian teratoma with immature neuroepithelial elements and no evidence of yolk sac tumour. A left pelvic sidewall nodule showed a deposit of immature teratoma, while all other sites of peritoneal disease showed mature teratomatous elements in keeping with peritoneal gliomatosis.

A follow-up CT-CAP 6 weeks post-surgery confirmed the presence of low-volume abdomino-pelvic disease. Both the gynaecologic oncology and germ cell multidisciplinary teams recommended an initial conservative active surveillance approach. The rationale behind this approach was based on postoperative normalisation of tumour markers, complete gross resection of the pelvic-confined immature component and the paucity of evidence for survival benefit in that context. Follow-up at five months post-surgery raised suspicion of disease relapse/



Graphic 1. Serum sodium and AFP level variation along the patient's treatment trajectory.

progression with a new 6 cm left paracolic gutter mass, a 10 cm anterior peritoneal mass, and increased soft tissue in the porta hepatis and subdiaphragmatic spaces. Serum alpha-fetoprotein levels rose to 1331 kunits/l (Graphic 1), leading to a recommendation for chemotherapy with three cycles of Bleomycin-Etoposide-Cisplatin (BEP) and potential surgical debulking.

The patient's first admission for chemotherapy was complicated by moderate ascites and severe hyponatremia (113 mmol/l), necessitating fluid restriction (1 l/day), hypertonic fluids, Tolvaptan administration (15 mg daily) and ascitic drainage.

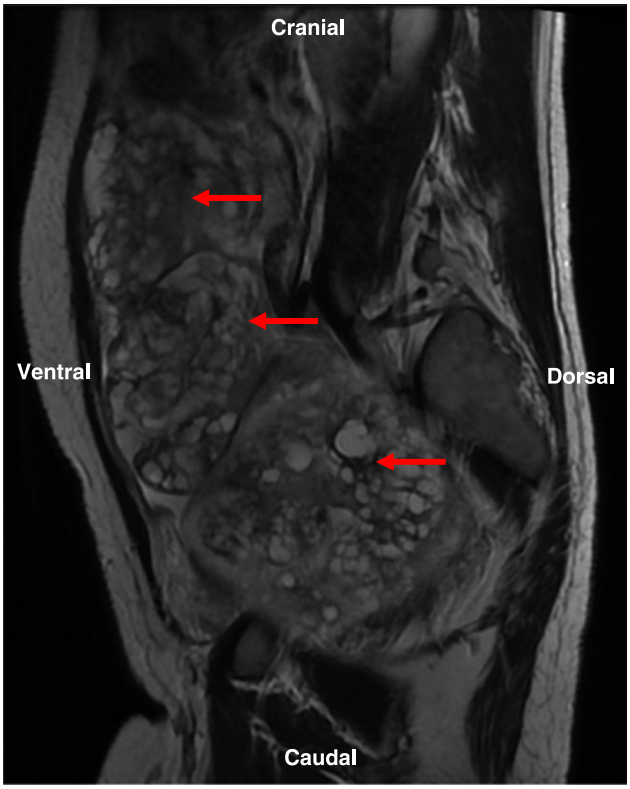


Figure 1. Sagittal view. Abdomino-pelvic MRI after surgery and three cycles Bleomycin-Etoposide-Cisplatin chemotherapy showing significant disease progression including an 11.3 cm porta hepatis mass, a 9.2 cm mass overlying liver segments 6 and 7, a 5.3 cm right subdiaphragmatic mass and a 16 cm pelvic mass (red arrows).

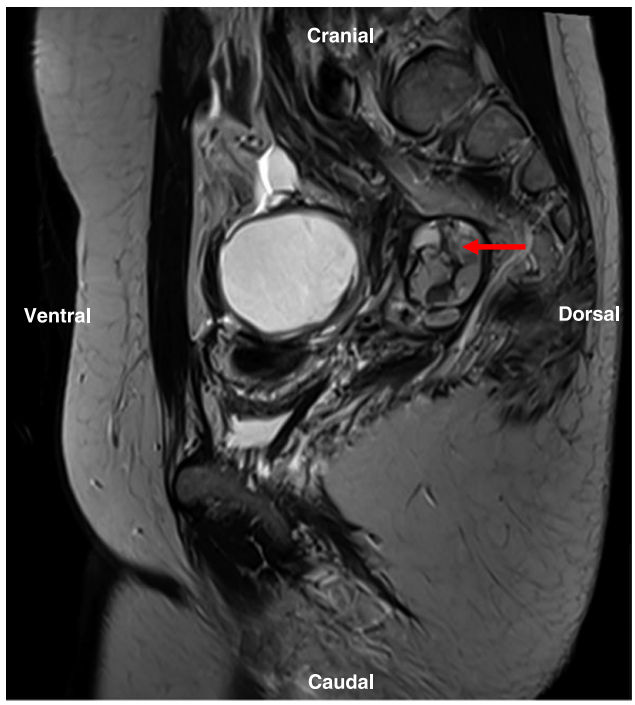


Figure 2. Sagittal view. Pelvic MRI showing slowly progressive residual/recurrent disease consisting of a 4×3 cm multiloculated cystic lesion containing fat in the pouch of Douglas (red arrow). A stable 8 mm subcapsular deposit overlying segment 7 of the liver was also noted—not seen on this image.

Table 1

Literature review—case reports of immature ovarian teratoma and paraneoplastic SIADH

References	Age	Symptoms	Serum Na +	Tumour markers	Diagnosis and staging	Treatment modality	Surgical findings and surgical approach	Recurrence	Resolution of hypo Na +
Lam *et al.*[17]	17	Low abdominal pain and 3-month amenorrhoea	115	AFP 39	Stage 1C, G2, immature teratoma	Surgery, Chemotherapy (cisplatin, vinblastine and etoposide)	10 cm tumour, small amount of peritoneal fluid. Right salpingo-oophorectomy and omental biopsy	No	Surgery
Lam *et al.*[14]	17	Low abdominal pain (1 month)	121	AFP 310CA-125 795	G2, immature teratoma	Surgery, Chemotherapy	x	No	x
Roman *et al.*[16]	22	Nausea, headache, 2 month amenorrhoea, abdominal pain	111	AFP 200	Stage 3, G2, immature teratoma + peritoneal gliomatosis	Surgery, Chemotherapy (BEP)	12 cm tumour, small amount of peritoneal fluid, peritoneal gliomatosis. Left salpingo-ophorectomy and peritoneal vegetations excision.	No	Surgery
Sakomoto *et al.*[11]	16	Low abdominal pain, bloating and constipation for months	119	AFP 131CA-125 345	Stage 1C, G2, immature teratoma	Surgery, Chemotherapy (BEP)	20 cm tumour, capsule rupture, little ascitic fluid, Right salpingo-oophorectomy, greater omentum segmental resection, mesentery lymph node biopsy	No	Surgery
Iqbal *et al.*[15]	12	2 year urinary incontinece, weight gain, abdominal distension, vomiting and night sweats	123	AFP 157CA-125 942	Stage 3B, immature teratoma + peritoneal gliomatosis	Surgery	20 cm tumour, ascitis. Right salpingo-oophorectomy + omentectomy + peritoneal stripping	x	Surgery
Tejani *et al.*[12]	32	2 months history of abdominal pain, nausea, weight gain, distension, early satiety, constipation, urinary frequency.	116	CA-125 244.9	Stage 1A, G2, immature teratoma + mature teratoma + gliomatosis peritonei	Surgery, Chemotherapy (BEP)	21.5 cm tumour, bilateral ovarian masses, ascites. Bilateral salpingo-ophorectomy + omentectomy + peritoneal sampling + pelvic lymph node dissection	No	Surgery
Hom-Tedla *et al.*[10]	27	3 months of abominal pain, nausea and vomiting, Fatigue, dizziness, blurred vision and headache.	116	AFP 69.3CA-125 191	Stage 3B, G2, immature teratoma + gliomatosis peritonei	Surgery, Chemotherapy (BEP)	20 cm tumour, ascitis (3L), multiple 2 mm nodules in omentum, pelvis and cut du sac. tumour resection, peritoneal nodules resection, omentectomy.	No	Surgery
Yuvaraj *et al.*[13]	15	Constipation and abdominal discomfort	119	AFP 12.2	Stage 3, G3, immature teratoma + gliomatosis peritonei	Surgery	16 cm tumour. Right salpingo-oophorectomy, left para-tubal cystectomy, biopsy of right diaphragm, rectal mass, omentectomy and peritoneal stripping	x	Surgery
Present case	26	3 months history of abdominal distension, early satiety, changes in bowel habits. abdominal pain and dizziness for 3 days.	113	AFP 100 CA-125 338 . Rise in AFP during FU to 1331 (in 5 months). Negative tumour markers after chemotherapy	Stage 3C, G2, immature teratoma + gliomatosis peritonei + growing teratoma syndrome	Surgery, ChemoTherapy (BEP), Surgery	22 cm tumour, ascites, peritoneal disease in abdomen and pelvis. R2 right salpingo-oophorectomy and omental biopsies. Recurrence - multi-sited 10–15 cm tumour. 2nd surgery R1. omentectomy resection of abdominal pelvic masses from sigmoid mesentery, base of liver, pouch of Douglas, and omentum. Stripping of right hemi-diaphragm, bladder peritoneum, pouch of Douglas peritoneum, right and left paracolic gutters.	Yes	Surgery and chemotherapy

BEP, Bleomycin-Etoposide-Cisplatin.

Despite initial successful sodium correction to 130 mmol/l, the patient developed intense vomiting and diarrhoea during her third chemotherapy cycle, which brought her sodium levels back down to 118 mmol/l. Despite an excellent response in serum alpha-fetoprotein (21.2 kunits/l) (Graphic 1), post-chemotherapy imaging showed significant disease progression including an 11.3 cm porta hepatis mass, a 9.2 cm mass overlying liver segments 6 and 7, a 5.3 cm right subdiaphragmatic mass and a 16 cm pelvic mass (Fig. 1).

A recommendation for cytoreductive surgery was made. Sodium levels were 125 mmol/l before surgery. A fertility-sparing procedure was performed, achieving an R1 resection. Surgery consisted of a midline laparotomy, omentectomy, resection of 10–15 cm masses from sigmoid mesentery, base of liver, pouch of Douglas, omentum, and resection of multi-site nodules of disease from the right hemi-diaphragm, bladder peritoneum and bilateral paracolic gutters. Small (<0.5 cm) deposits were left on small bowel mesentery and left ovary. Six days post-surgery, the patient was discharged with a sodium level of 138 mmol/l.

Histology revealed metastatic mature teratoma, consistent with a GTS. The patient, symptom-free since the second surgery, has been under joint follow-up by the medical oncology and surgical gynae-oncology teams. One year later, a surveillance pelvic MRI indicated slowly progressive residual/recurrent disease consisting of a 4×3 cm multiloculated cystic lesion containing fat in the pouch of Douglas and a stable 8 mm subcapsular deposit overlying segment 7 of the liver (Fig. 2). Two years post-initial presentation, tumour markers and serum sodium levels remain normal, and the patient experiences no signs of menopause. She is currently on a 3-monthly follow-up protocol with examination, serum tumour markers including AFP, with a plan to proceed to cross-sectional imaging if there are any suspicious findings.

Clinical discussion

This report outlines a rare gynaecological tumour, immature teratoma, which exhibited an uncommon presentation involving gliomatosis peritonei with associated paraneoplastic hyponatremia. Remarkably, the patient developed a growing teratoma syndrome after undergoing chemotherapy, and hyponatremia persisted until a second surgical intervention.

In reviewing existing literature, only eight reported cases document hyponatremia as a paraneoplastic syndrome secondary to immature ovarian teratoma (Table 1), with our case being the first published in the United Kingdom. Previous cases have shown resistance to medical sodium correction, with resolution occurring solely post-surgery, indicating a probable ectopic secretion of ADH or a vasopressin-like peptide by the tumour and its implants.

Neuroendocrine tissue within the teratoma is thought to be the primary source of ADH secretion[19]. Taksin *et al.*[20], outlined the presence of membrane-bound neurosecretory granules in undifferentiated tumour cells as the primary driver of ADH secretion. Sakomoto *et al.*[11] notes that the neuroepithelium present within an immature teratoma with a specific antibody for ADH is the driver for ectopic vasopressin secretion. A common feature among all cases of immature ovarian teratomas presenting with paraneoplastic SIADH is their large proportion of immature neuroepithelium within the tumour; all these tumours were classified as greater than or equal to grade 2 immature teratomas. This observation indicates that vasopressin is likely to be secreted by the immature neuro-elements of the tumour and its deposits.

In our case, we encountered refractory hyponatremia in the context of a growing teratoma syndrome. After three cycles of chemotherapy hyponatremia remained, only resolving after the second surgical procedure. Given that histopathology of the resected specimens only reported mature elements, one may hypothesise that not only immature but also mature glial tissue may secrete ADH or a vasopressin-like substance.

From a different perspective, chemotherapy, coupled with vomiting and diarrhoea, may have contributed to the low sodium levels prior to surgery. Cisplatin, an antineoplastic agent, is also known to induce hyponatremia. After the second surgical intervention, where only mature elements were resected, no new hyponatremic episodes occurred, supporting the effectiveness of chemotherapy in eliminating immature components that could have been causing hyponatremia.

The diagnosis of SIADH is one of exclusion and was confirmed through comprehensive testing, meeting Schwartz's criteria[21]. Notably, the patient's euvolemic hyponatremia resolved with tumour resection, affirming SIADH as likely secondary to ectopic tumour secretion of ADH.

A limitation of this case study is the lack of direct measurement of serum vasopressin. When interpreting sodium levels, one must be careful and aware of possible confounding factors that may impact sodium levels, such as vomiting, diarrhoea, laxatives use and cisplatin chemotherapy.

Conclusion

Hyponatremia, a rare paraneoplastic syndrome, may occur in patients with immature ovarian teratomas. Abdominal symptoms and hyponatremia warrant pelvic examination to rule out ovarian tumours. Surgical intervention may be crucial for resolving hyponatremia in suspected immature teratomas.

Ethical approval

Ethical approval was not required for this case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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No funding was acquired for this case report.

Author contribution

A.R.M.: wrote the manuscript. M.B.: involved in case management, reviewed manuscript. S.Z.: contributed to manuscript writing, obtained patient's consent. M.S.: involved in case management, reviewed manuscript. J.D.: supervisor. involved in case management, reviewed manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Ana Rita Mira.

Data availability statement

No datasets generated for this case report.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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