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Atypical Location of a Granulosa Tumeur: A Case Report and Review of the Literature

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Abstract

Context: *Granulosa tumours account for 5% of ovarian malignancies and are the most common of the sex cord and stromal tumours . The adult form is the most common (95%). Adult granulosa tumours have few specific features apart from signs of hyperoestrogenism, increased inhibin B/AMH and Foxl2 mutation. These tumours have a good prognosis and require optimal surgery. However, the sometimes late relapses require close monitoring.*

Observation: *This is a 60 year old multiparous patient who underwent undocumented pelvic surgery in 2009 and consulted for abnormal uterine bleeding. Pelvic ultrasound and abdomino- pelvic CT scan revealed a left latero-uterine mass, a mass in the abdominal wall and endometrial thickening. The patient underwent an exploratory laparotomy. The procedure consisted of a left hysterectomy and adnexectomy (right adnexa not found), and resection of the abdominal mass. Anatomopathology, immunohistochemistry and FoxL2 mutation testing concluded that the tumour was a granulosa tumour in the abdominal wall. Following the multidisciplinary meeting, the decision was made to discuss adjuvant chemotherapy and to establish close monitoring by tumour markers.*

Conclusion: *Our case highlights the difficulties in the diagnosis of adult granulosa tumours. The present study reviews diagnostic methods, histological features and therapeutic recommendations.*

Introduction

Stromal tumours of the sex cords of the ovary are rare (3-5% of all ovarian malignancies). Granulosa cell tumours (GCTs) account for 70-90% of these tumours **[**1**]**. The two subtypes are differentiated by their clinical and histopathological features. The more common adult granulosa cell tumours (AGCT) have the following characteristics: onset around or after the perimenopausal period, early detection, hyperestrogenism **[**1,2**]** and association with a FOXL2 gene mutation **[**3**]**. Early stage or complete cytoreductive surgery is indicative of a better prognosis.

With a relatively indolent behaviour, the tumour sometimes recurs several years after the initial diagnosis. There is no consensus on adjuvant treatment or post-operative monitoring, partly because of the low incidence of this tumour. Recurrences can occur at different stages and mainly involve the abdominopelvic cavity **[**1,2**]**. As AGCT rarely presents with alarming elevations of specific tumour markers or causes troublesome symptoms such as increasing ascites, the management of recurrent AGCT can be difficult. We present a case of relapsed AGCT detected by imaging studies and currently undergoing chemotherapy.

Observation

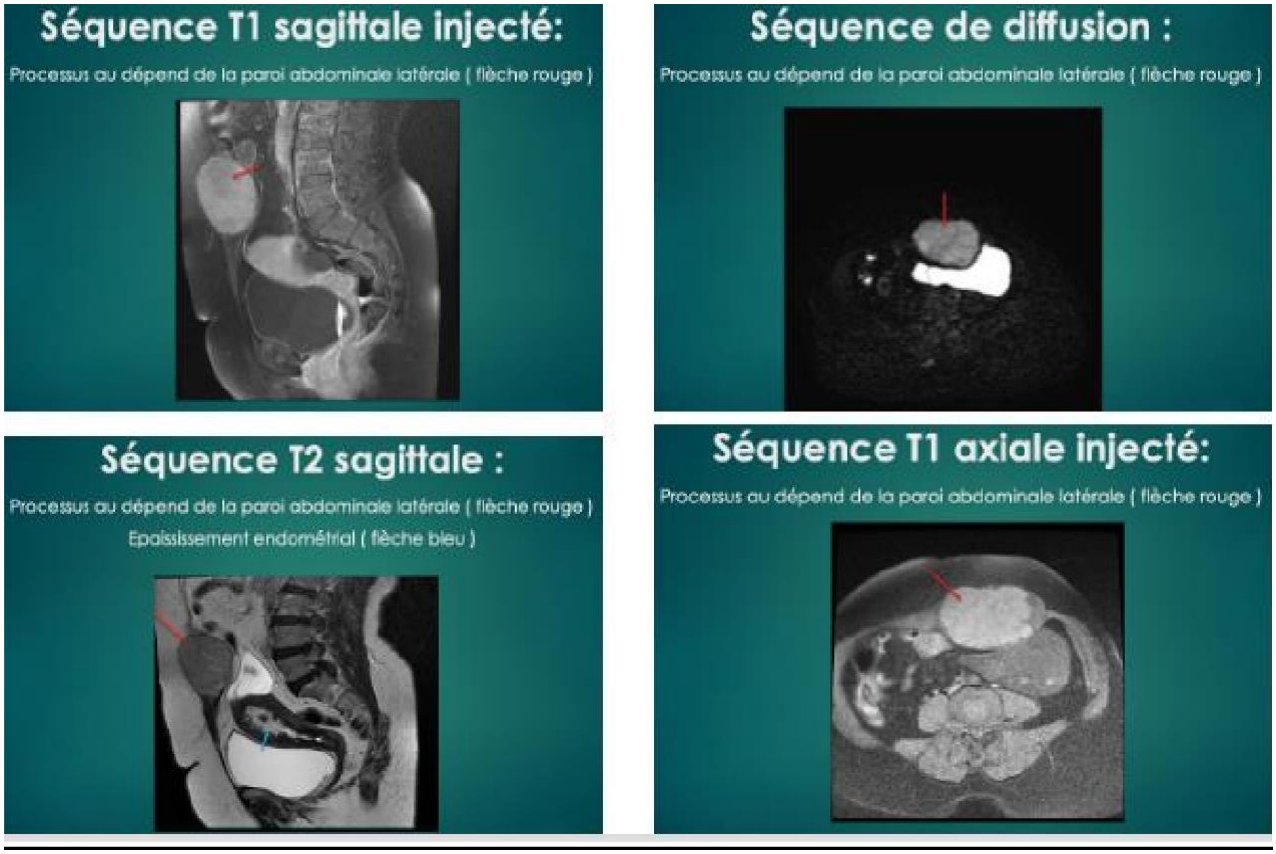
We report the case of Mrs H.Z, 60 years old, multiparous (7EV/AVB), postmenopausal, followed for hypothyroidism on levothyrox for 02 months, operated in 2009 for an undocumented right latero-uterine mass who was initially admitted for management of postmenopausal metrorrhagia.

The initial clinical examination found a conscious patient, hemodynamically and respiratorily stable, and the gynecological examination was unremarkable except for the presence of an abdominal mass measuring 7 cm in long axis and appearing to be dependent on the rectus.

Ultrasound revealed a left latero-uterine mass measuring 15x16x10 cm, associated with endometrial thickening measured at 20mm, and a parietal mass appearing to be dependent on the right rectus measuring 7cm long.

Abdominal-pelvic MRI showed a thickened and irregular endometrium measuring 21mm in maximum thickness with the presence of a left latero uterine mass in hypo T1 hypersignal T2 unenhanced after injection of contrast medium and unrestricted thin walled lobulated without septum or vegetation of homogeneous signal measuring 150x 142x95mm associated with the presence at the level of the left lateral sub umbilical abdominal wall of an oval formation well limited encapsulated in hypoT1 signal

and T2 iso-signal strongly enhanced after injection of contrast medium measuring 89x58x91mm suggesting in the first instance a fibrous tumour.



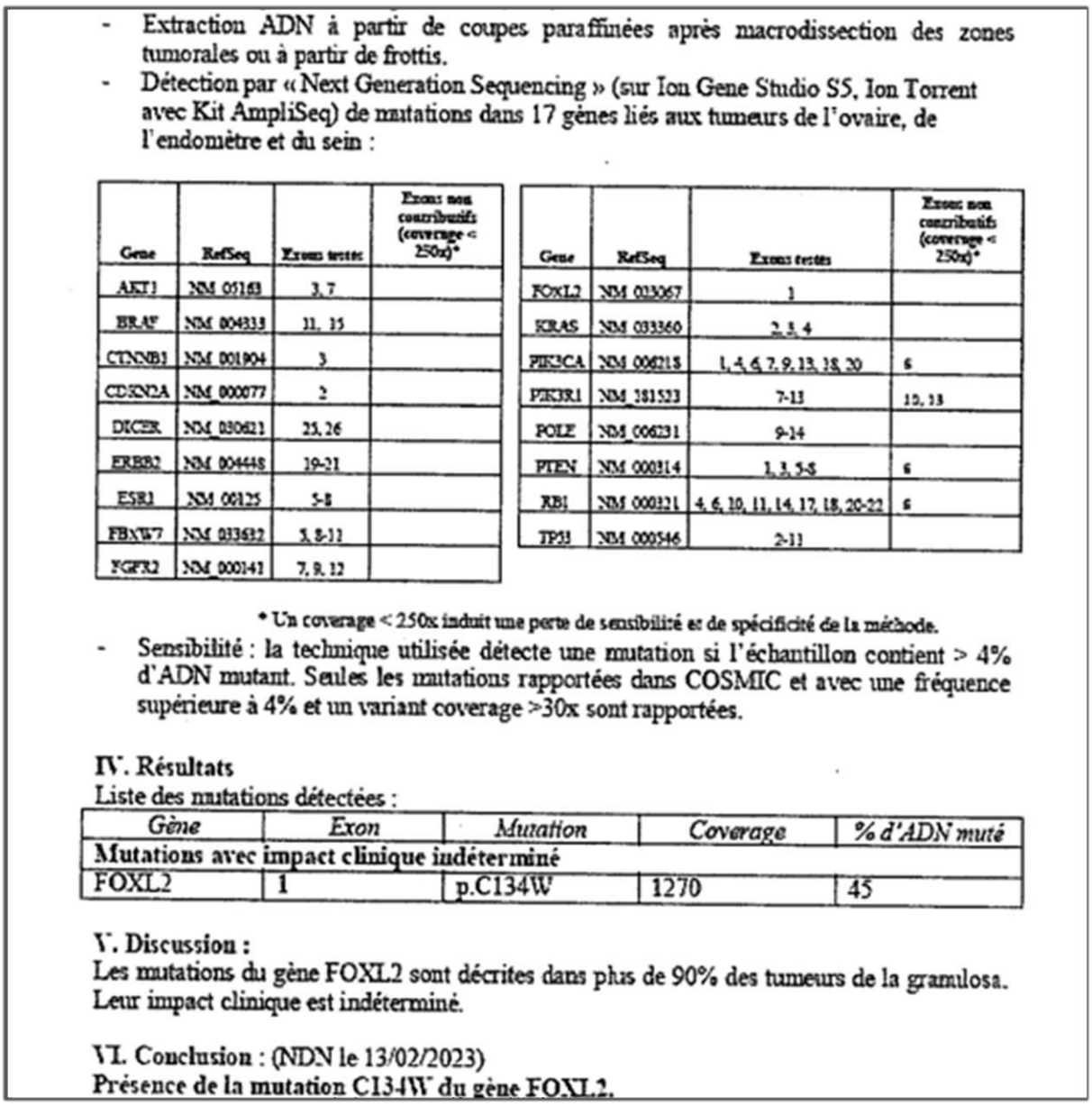
Different sections showing the parietal mass at the expense of the rectus

The patient underwent a diagnostic hysteroscopy and then surgery with anatomical study of the presence of foci of complex atypical hyperplasia, given the symptomatology and thickening observed on ultrasound and MRI.

An exploratory laparotomy was performed and revealed a left parietal paral mass 10 cm long, adherent to the rectus abdominis muscle, an enlarged uterus 10 SA and a flaccid left latero-uterine cystic mass adherent to the uterus and the bowels 15 cm long. The right adnexa was not found during the exploration (probably resected in 2014).

We proceeded to resect the parietal mass and then performed a total hysterectomy with left adnexectomy and cystectomy.

The definitive pathological study of the mass which developed opposite the rectus came back in favour of a tumour of the granulosa confirmed by immunohistochemical and molecular study. Polypoid hyperplasia of the entire endometrium with foci of complex atypical hyperplasia were found on the hysterectomy specimen. The left ovary was unremarkable except for a simple serous cyst.



- Extraction ADN à partir de coupes paraffinées après macrodissection des zones tumorales ou à partir de frottis.
- Détection par « Next Generation Sequencing » (sur Ion Gene Studio S5, Ion Torrent avec Kit AmpliSeq) de mutations dans 17 gènes liés aux tumeurs de l'ovaire, de l'endomètre et du sein :

Gene	RefSeq	Exons testés	Exons non contributifs (coverage < 250x)*
AKT1	NM_05163	3, 7	
BRAF	NM_004333	11, 15	
CTNNB1	NM_001904	3	
CDKN2A	NM_000077	2	
DICER	NM_030621	25, 26	
ERBB2	NM_004448	19-21	
ESR1	NM_00125	5-8	
FBXW7	NM_033632	5, 8-11	
FGFR2	NM_000141	7, 9, 12	

Gene	RefSeq	Exons testés	Exons non contributifs (coverage < 250x)*
FOXL2	NM_023067	1	
KRAS	NM_033360	2, 3, 4	
PIK3CA	NM_006218	1, 4, 6, 7, 9, 13, 18, 20	6
PIK3R1	NM_181523	7-13	10, 13
POLE	NM_006231	9-14	
PTEN	NM_000314	1, 3, 5-8	6
RB1	NM_000321	4, 6, 10, 11, 14, 17, 18, 20-22	6
TP53	NM_000546	2-11	

* Un coverage < 250x induit une perte de sensibilité et de spécificité de la méthode.

- Sensibilité : la technique utilisée détecte une mutation si l'échantillon contient > 4% d'ADN mutant. Seules les mutations rapportées dans COSMIC et avec une fréquence supérieure à 4% et un variant coverage >30x sont rapportées.

IV. Résultats

Liste des mutations détectées :

Gène	*Exon*	*Mutation*	*Coverage*	*% d'ADN muté*
Mutations avec impact clinique indéterminé				
FOXL2	1	p.C134W	1270	45

V. Discussion :

Les mutations du gène FOXL2 sont décrites dans plus de 90% des tumeurs de la granulosa. Leur impact clinique est indéterminé.

VI. Conclusion : (NDN le 13/02/2023)

Présence de la mutation C134W du gène FOXL2.

Result of the molecular study for FOXL2 mutation

Discussion

Although AGCT has a low potential for malignancy, it is described as recurrent in 20-25% of patients, with an average of 4-6 years between initial treatment and recurrence. Several reports have suggested checking serum levels of oestradiol, human chorionic gonadotropin, alpha- fetoprotein, lactate dehydrogenase, inhibin and anti-mullerian hormone (AMH) **[**4-5**]**.

While a meta-analysis of 70 AGCT cases and 351 controls demonstrated that serum AMH was a useful biomarker **[**5**]**, a series of AGCT cases (n = 30) did not find a relationship between serum oestradiol and disease recurrence **[**6**]**. Serum inhibin levels, in contrast, are readily available as a routine clinical laboratory test.

Efforts have been made to identify predictive features of recurrence, such as age, initial tumour stage, tumour size and residual tumour **[**2-3**]**. A retrospective study using the National Cancer Database 1998-2013 for ovarian AGCT (n = 2680) showed that older age, more comorbidities, previous tumour, higher grade, higher stage, larger tumour size, incomplete surgical staging and residual disease at the surgical margin were independently associated with a higher risk of death **[**7**]**. As AGCT rarely induces prominent symptoms, imaging findings of any new or enlarging lesion should raise alarm and require further investigation.

Most systemic reviews or population-based studies have not found a benefit to postoperative adjuvant chemotherapy or radiotherapy **[**2,7,10**]**. Five patients with GCT (4 AGCT, 1 juvenile GCT) were treated with the PD-1 inhibitor pembrolizumab in a phase II trial, but unfortunately no objective response was observed, although two patients had stable disease for ≥12 months **[**11**]**. In a Gynecologic Oncology Group phase II trial of bevacizumab in recurrent ovarian sex cord tumours (32 GCTs, 4 unclassified SCSTs), 16.7% of patients achieved a partial response and 77.8% had stable disease **[**12**]**.

Conclusion

In the light of this work, we aim to add to the literature regarding the early management of recurrent AGCT, which remains early detection and surgical intervention. Laboratory data should be integrated with caution, as recent data have not indicated a specific tumour marker suitable for serial follow-up. Imaging studies, such as ultrasound, CT, PET and others, should be performed routinely and whenever recurrence is suspected. There is an urgent need for further studies on AGCT to assess the long-term efficacy of endocrine therapies, but also of other therapeutic agents, and to establish biomarkers for monitoring responses.

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