International Journal of Surgery Case Reports 102 (2023) 107842

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Case report

# Different clinocopathological presentations of steroid cell tumour – Report of three rare cases

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ARTICLE INFO

*Keywords:*
Case report rare tumours
Androgen-secreting
Uncertain malignant behaviour
Different clinical presentations

ABSTRACT

*Introduction and importance:* We present three cases of steroid cell tumour due to their rarity, their differing clinical presentations and the distinct pathology.

*Case presentation:* Case 1: A 50-year-old female presented with heavy menstrual bleeding. Adenomyosis and multiple leiomyomata were found along with an incidental 2.5mm, paratubal steroid cell tumour. Given the size of the tumour and the histopathological features this was considered benign.

Case 2: A 69-year-old female patient presented with virilization, found to have a left ovarian steroid cell tumour. Since there was capsular infiltration, close follow up was advised.

Case 3: A 35-year-old female patient presenting with an acute abdomen due to torsion of a 15 cm right ovarian mass. The mass showed immunomorphological features of a steroid cell tumour. Since this tumour was large and had features of necrosis, high mitotic activity and nuclear pleomorphism, it was regarded as malignant.

*Clinical discussion:* Steroid cell tumours of the ovary are rare (<0.1 % of all ovarian neoplasms) with uncertain malignant behaviour and are difficult to diagnose especially if classical virilising symptoms are absent.

*Conclusion:* Thorough histopathological analysis and immunohistochemistry are essential in arriving at a definite diagnosis when the classical presentation is absent.

## 1. Introduction

Ovarian steroid cell tumours (SCT), not otherwise specified (NOS), are rare sex cord-stromal tumours with malignant potential, accounting for <0.1 % of all ovarian tumours [1]. The tumours can occur at any age with a mean age of 43 years, which is younger than other steroid tumours, they rarely occur before puberty. Among the patients affected with SCT-NOS, 56–77 % have symptoms of androgenic changes, such as hirsutism and virilization including acne, clitoral enlargement, deepening of the voice, and alopecia. 6–23 % have estrogenic manifestations such as menorrhagia, postmenopausal bleeding, or even endometrial carcinoma. Only 6–10 % are clinically associated with Cushing's syndrome, and 25 % of SCT-NOS are nonfunctioning. Most of these tumours are benign, however, clinically malignant behaviour occurs in 25–40 % of the patients. This is usually within the peritoneal cavity and rarely at distant sites [2]. A case series from Massachusetts General Hospital, demonstrated 94 % of the tumours were unilateral and 28.6 % were malignant [3].

Hayes and Scully have identified five pathological predictive characteristics of malignancy as follows: two or more mitotic figures/ten high-power fields (malignancy in 92 %), necrosis (malignancy in 86 %), a diameter of >7 cm (malignancy in 78 %), haemorrhage (malignancy in 77 %), and grade 2 or 3 of nuclear atypia (malignancy in 64 %) [4].

This report describes three cases of these rare steroid cell tumours (NOS) with different clinical presentations and distinct histopathological features. These include an asymptomatic incidental tumour, a tumour with typical hormone-related symptomatology and a tumour with malignant behaviour and with no obvious androgenic manifestations.

Aspects of the presentation, differential diagnosis and treatment of these tumours are described as per SCARE guidelines [5].

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https://doi.org/10.1016/j.ijscr.2022.107842
Received 22 September 2022; Received in revised form 13 December 2022; Accepted 15 December 2022

## 2. Presentation of cases

### 2.1. Case 1

A 50-year-old woman presented with heavy menstrual bleeding. There was ultrasound evidence of leiomyomata and a right ovarian, thin-walled cyst of 3.9 × 2.4 × 3.5 cm. Ca125 levels were 9.7 kU/L (normal values 0.0–35.0). A total abdominal hysterectomy with bilateral salpingo-oophorectomy was undertaken by gynaecological surgeon for treatment of symptomatic fibroids. Histology revealed adenomyosis, leiomyomata and ovarian follicular cysts. There was incidental finding of a solid round tumour 2.5 mm at the fimbrial end of the left tube (Fig. 1a). This tumour was composed of large cells with small round nuclei and copious eosinophilic cytoplasm, many of which contain ceroid pigment (Fig. 1b, c). These findings appear to represent an incidental small steroid cell tumour.

Since this was a benign tumour and an incidental finding, no follow up was recommended. However, blood exams were done for unrelated reasons and were unremarkable. There is no evidence of recurrence to this date.

### 2.2. Case 2

A 69-year-old presented with virilisation symptoms, which included deepening of her voice, frontal balding and clitoromegaly. Laboratory findings included normal blood cell count, electrolyte, renal, bone and hepatic profile. Hormonal profiling was as follows: testosterone levels were elevated (46.9 nmol/L; reference range 0.1–1.4), with normal levels of cortisol, DHEAS, CA125, Sex Hormone Binding Globulin, Growth Hormone, Androstenedione, 17-Hydroxy-Progesterone and dihydrotestosterone. The MRI scan of the pelvis showed a left ovarian heterogeneous mass measuring 4 cm with restricted diffusion. She underwent a laparoscopic bilateral salpingo-oophorectomy. The macroscopic examination revealed a fragmented ovary and a detached yellowish nodule measuring 40 × 30 × 26 mm with a smooth and shiny surface. Cut surface revealed vaguely nodular appearance with tiny brownish foci intermingled with yellowish areas.

Microscopy showed a nodule composed of sheets of monomorphous cells with rounded or oval nuclei and abundant eosinophilic cytoplasm. Scattered neoplastic cells showed a pale and strikingly vacuolated cytoplasm (Fig. 1d). There was no significant pleomorphism, increased mitotic activity, necrosis or haemorrhage identified. A focus suspicious of lymphovascular space invasion was seen (Fig. 1e). Focal capsular invasion was present (Fig. 1f). Mitotic activity was low as 1 mitoses/10 HPF. The immunohistochemistry shows strong diffuse positivity for Calretinin (Fig. 1g), Inhibin (Fig. 1h) and CD99 (Fig. 1i) and negativity for HMB-45, Melan-A, S-100 and AE1/AE 3. Proliferative activity, as evaluated by Ki-67, was up to 3 %. The overall features were suggestive of a steroid cell tumour, NOS. The fallopian tubes and contralateral ovary had normal morphology. The case was later reviewed at the supraregional MDT were a diagnosis of steroid cell tumour, NOS, was confirmed with capsular invasion but no convincing lymphovascular invasion.

Since there was capsular infiltration, follow up with surveillance of testosterone levels, cross sectional imaging, and clinical examination was recommended. However, since the tumour was confined to ovary, no adjuvant treatment was advised. Her symptoms of virilisation improved after two years. Currently she is well and asymptomatic. On the most recent MRI from 5th of October 2022, there was no evidence to suggest local recurrence. Blood exams were unremarkable with testosterone levels of <0.4 nmol/L.

### 2.3. Case 3

A 35-year-old presented with pressure symptoms and a palpable lump at lower abdomen, over the past month. Her full blood count was normal a part of slightly increased WBC and RbC (10.9 × 109/L and 4.861012/L; reference range 4.0–10.0 and 3.80–4.80), thyroid profile as well as FSH, LH, Prolactin, testosterone, HCG and CA125 levels were normal. On examination, a large soft, non-tender mass was found at

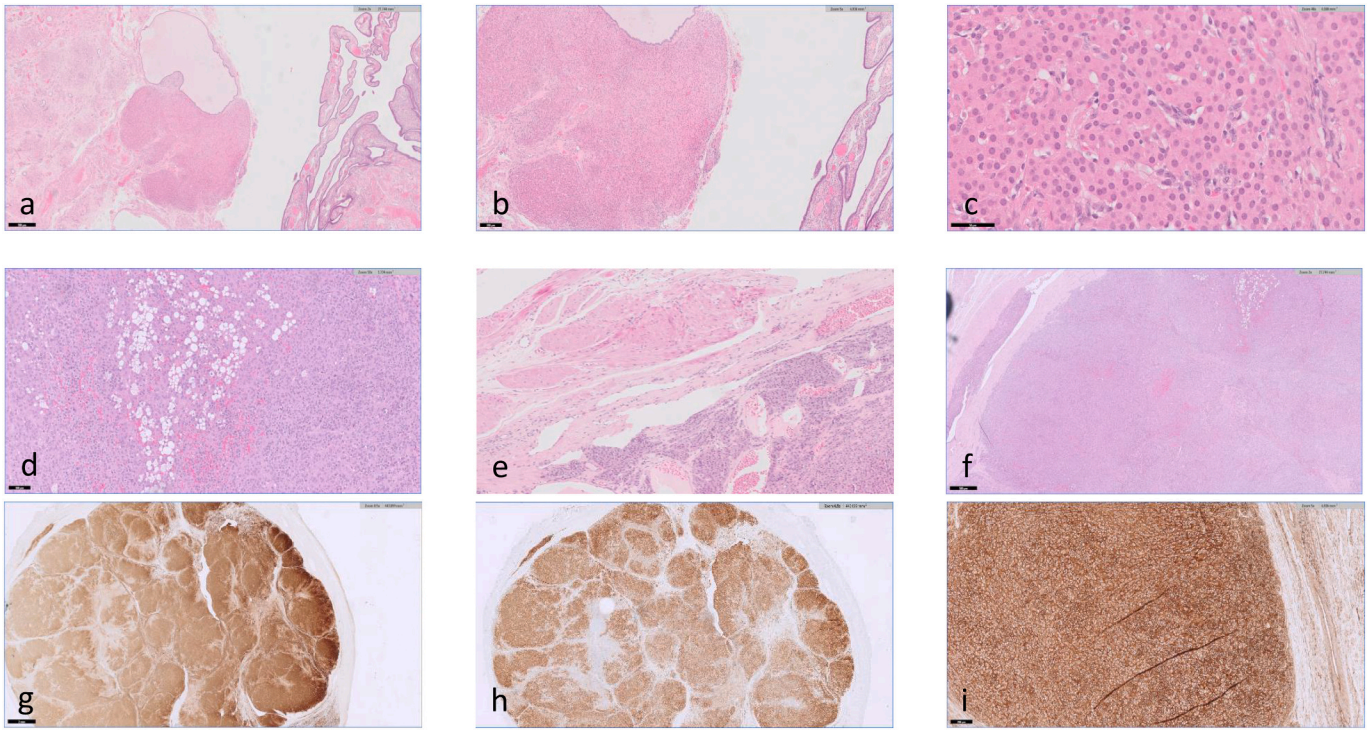


**Fig. 1.** Case 1: Incidental finding at the fimbrial end, H&E ×2 (a); Large cells with small round nuclei and copious eosinophilic cytoplasm, H&E ×5 (b) and H&E ×40 (c). Case 2: Scattered neoplastic cells showing a pale and strikingly vacuolated cytoplasm, H&E ×10 (d); Focal capsular invasion, H&E ×5 (e); Focus suspicious of lymphovascular space invasion, H&E ×2 (f); The immunohistochemistry shows strong diffuse positivity for Calretinin, ×0.5 (g), Inhibin, ×0.5 (h) and CD99, ×0.5 (i).

central lower abdomen extending above the umbilicus. A CT confirmed a large centrally cystic/necrotic mass in the pelvis extending into the lower abdomen, 10 × 13 × 16.5 cm. This was surrounded by a small amount of free fluid in the presacral space. A midline laparotomy was performed and a 16 cm, torted right ovarian mass was noted. A right side salpingo-oophorectomy and omental biopsy was taken.

Macroscopically a 4 cm long Fallopian tube with attached ovarian mass 15 × 10 × 5 cm, which had a lobulated external appearance with intact capsule was noted. Slicing revealed pale yellow tissue, which was solid and had a nodular architecture with scattered cystic areas. There were also areas of haemorrhage up to 6 cm. The omentum appeared normal.

Histology showed a neoplasm with a low power nodular architecture. Multiple nodules were present with a predominantly diffuse architecture but with focal nested and corded arrangements. The tumour cells showed abundant eosinophilic cytoplasm. The nuclei were largely quite uniform but there were scattered quite markedly atypical nuclei. Multiple small areas of necrosis were present (Fig. 2a, b) and there was significant mitotic activity with several mitoses within a single high-power field (Fig. 2c). No evidence of lymphovascular invasion was identified.

Immunohistochemically there was diffuse positive staining with Calretinin (Fig. 2d), CD99 (Fig. 2e) and Inhibin (Fig. 2f) and focal staining with CK7. Occasional cells were positive with MNF116 and EMA. WT1, PAX8 and GATA3 were negative. A reticulin stain showed deposition around nests of tumour cells and individual cells (Fig. 2g). Initially a diagnosis of sclerosing stromal tumour (SST) was proposed. Since this tumour showed adverse features, an expert opinion was sought and it was concluded that the overall appearances were in keeping with a steroid cell tumour, NOS with potentially malignant behaviour. Currently, patient is well but always worried that the tumour may recur. CT scan from November 2022 showed no evidence of any recurrence. However, patient asked and subsequently has been referred for hysterectomy and left salpingo-oophorectomy as concerned about malignant potential of tumour.

Tabular representation of clinicopathological parameters and follow-up results for the cases is summarised in Table 1.

## 3. Discussion

Ovarian steroid cell tumours were first described by Scully, who reported 63 cases ranging from 2 to 80 years of age [4]. Steroid cell tumours have been previously classified into three subtypes NOS, Leydig cell tumour and stromal luteoma [6]. Main differential diagnosis of steroid cell tumours is with sex cord stromal tumours. Pure sex cord tumours (adult granulosa cell tumour, juvenile granulosa cell tumour, Sertoli cell tumour and sex cord tumour with annular tubules) and mixed sex cord stromal tumours (Sertoli-Leydig cell tumour, sex cord stromal tumour NOS and gynandroblastoma) as well as fibroma, thecoma, microcystic stromal tumour and signet ting stromal tumour are excluded *a priori*, based on morphology and immunoprofile. In the first case an adrenal rest was considered since it is commonly found as an incidental finding near the adnexa. Since the cells also have eosinophilic to clear cytoplasm and bland nuclei, the distinction is rather difficult. Immunohistochemistry is of limited value; however, the histopathology of adrenal rest would show the normal adrenal cortical and rarely medullary components. In this case, adrenal rest was disregarded on morphology. Stromal luteoma was also considered, as this proliferation was also composed of polygonal eosinophilic cells. This tumour is now under steroid cell NOS category [7]. However, stromal luteoma is most commonly located in the ovarian stroma, usually measuring <1.0 cm and frequently occurring in association with stromal hyperthecosis and with the presence of degenerative pseudovascular spaces containing red blood cells. Pregnancy luteoma is most commonly multifocal, occurs bilaterally in approximately one-third of the patients and usually regresses after the pregnancy [8].

In the second case a Leydig cell tumour was considered. Leydig cell tumours are usually small, with the average size of 2 cm and they typically present in the hilar location with associated Leydig's cell hyperplasia. Clustering of nuclei and eosinophilic nuclear free zones are typical features of this entity. The tumour cells contain cytoplasmic rod-shaped eosinophilic crystals/Reinke crystals. Nuclei are typically round with a single prominent nucleolus. Fibrinoid necrosis of blood vessels is also a feature. Immunohistochemical markers, Inhibin and Calretinin are quite useful in differentiating this tumour from other non sex cord tumours. However, there are no immune markers to differentiate Leydig cell tumours from steroid cell tumours, NOS [9].

However, in this case, there was no evidence of crystalloid, nuclear clustering or vasculopathy to suggest a Leydig cell tumour and hence diagnosis of steroid cell tumour, NOS was made. The tumour infiltrated through the capsule, but mitotic activity was only 1/1O hpf and the proliferation index, evaluated with Ki-67, was 3 %. There was no definite necrosis though haemorrhage was seen. The tumour was completely excised. However, these features cannot be used to predict behaviour accurately, and follow up with serum testosterone is recommended.

Initially for the third case the appearances favoured a diagnosis of sclerosing stromal tumour (SST). SST usually occurs in the second and third decades of life and typically presents with symptoms related to a

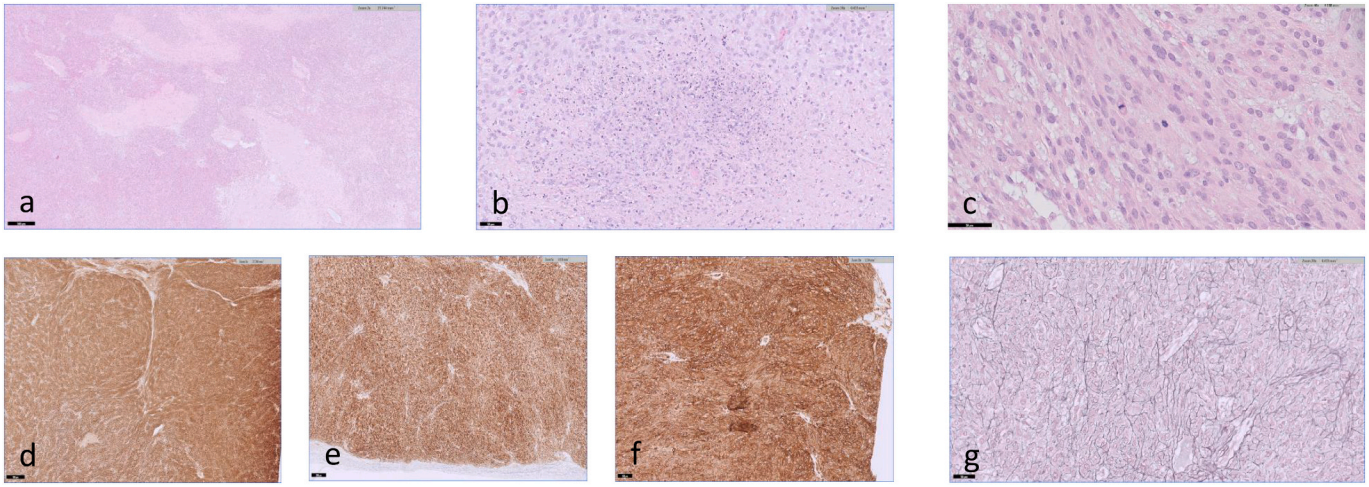


**Fig. 2.** Case 3 Areas of necrosis, H&E ×2 (a) and H&E ×20 (b); Mitosis, H&E, ×40 (c); The tumour cells show strong, diffuse expression of Calretinin, ×2 (d), CD99, ×5 (e), Inhibin, ×10 (f); Reticulin stain shows deposition around nests of tumour cells and individual cells, ×20 (g).

**Table 1**
Tabular representation of date related to the three cases of steroid cell tumours with clinico-pathological findings and post-operative outcome.

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Age | 50 | 69 | 35 |
| Clinical findings | Heavy menstrual bleeding | Virilisation symptoms - deepening of her voice, frontal balding, clitoromegaly | Feeling a heavy sensation with a palpable lump at lower abdomen. On examination, a large soft, non-tender mass. |
| Pre-op testosterone level | Not done | Elevated | Normal |
| Imaging | US pelvis: Right ovarian, thin-walled cyst of 39 × 24 × 35 mm identified, however, the lesion concerned was not detected. | MRI scan pelvis: Left ovarian mass measuring 40 mm | CT abdomen: Large centrally cystic/ necrotic abnormality in the pelvis extending to lower abdomen, 100 × 130 × 165 mm. |
| Type of surgery | Hysterectomy and bilateral salpingo-oophorectomy | Laparoscopic bilateral salpingo-oophorectomy | Right side salpingo-oophorectomy and omental biopsy done. Operative finding: 160 mm twisted right ovarian mass |
| Gross findings | Incidental finding of a solid round tumour 2.5 mm at the fimbrial end of the left tube | A fragmented ovary and a detached yellowish nodule measuring 40 × 30 × 26 mm. | An ovarian mass, 150 × 100 × 50 mm with lobulated external appearance and an intact capsule; cut surface nodular, pale yellow; solid with a few scattered cysts. |
| Microscopy | Small rounded tumour composed of large cells with round nuclei and copious eosinophilic cytoplasm with ceroid pigment. | The tumour was composed of sheets of monomorphous cells with rounded/ oval nucleus and abundant eosinophilic cytoplasm. Several cells showed strikingly vacuolated cytoplasm. No pleomorphism, increased mitotic activity, necrosis or haemorrhage. Focus suspicious of lymphovascular invasion seen. MF 1/10 HPF. Focal capsular invasion present. | The tumour comprised of solid sheets and lobules of epitheliod and spindled cells with abundant eosinophilic cytoplasm and vescicular nuclei showing moderate pleomorphism. The intervening stroma was hypocellular and oedematous. There were multiple small foci of necrosis. MF 4/ 10 HPF. There was no evidence of capsular invasion. |
| Positive IHC | Not done | Calretinin, Inhibin, CD99; Ki 67 ~ 3 % | Calretinin, Inhibin, CD99, Reticulin |
| Negative IHC | Not done | HMB-45, Melan A, S-100, AE1/AE3 | CK MNF 116, EMA, GATA 3, PAX 8, WT1 |
| Overall impression of the behaviour of the tumour | Benign | Since there was capsular infiltration, a close follow up was advised. | Since this tumour was large, necrotic, with high mitotic activity and nuclear pleomorphism, it was regarded as malignant. |
| Follow up | No follow up was recommended | Confined to ovary so no adjuvant treatment recommended. Suggested surveillance with testosterone, cross sectional imaging and clinical examination. Two years after surgery, virilisation symptoms improved. Currently patient is well and asymptomatic, with no evidence of recurrence. | Close monitoring with imaging. Currently patient is well and asymptomatic, with no evidence of recurrence on recent CT scan. However, patient requested hysterectomy and left salpingo-oophorectomy as concerned about malignant potential of tumour. |
| Post op testosterone levels | Not done | <0.4 | Not done |

pelvic mass or abnormal uterine bleeding. Oestrogenic and androgenic manifestations are rare, but virilisation and precocious puberty have been reported. Characteristic histological finding of ovarian SST is the pseudolobular pattern that is formed by the cellular nodules that are separated from each other by hypocellular, oedematous and collagenous stroma. The hemangiopericytomatous pattern-like dilated vascular structures are the characteristics of cellular areas, and the luteinised theca-like cells with vacuolised cytoplasm and fusiform fibroblast-like cells are the characteristics of hypercellular areas [10]. These tumours are Calretinin, Inhibin, ER, PR, CD10, Vimentin and SMA positive and Cytokeratin and EMA negative. Reticulin stain was reported to show a mild increase in reticulin fibers around blood vessels [11]. Mitotic activity is low but significant number of mitoses is seen in small subset of cases [12]. Since it was not a common tumour and in view of the presence of necrosis and significant mitotic activity, an expert opinion was sought. A diagnosis of SST was considered; however, these tumours only rarely exhibit such marked luteinisation of the cells and that usually happens in pregnancy. High mitotic activity was also unusual in an SST. It is also uncommon for these tumours to be so diffusely positive with Inhibin and Calretinin. Given the morphology and immunophenotype, a diagnosis of steroid cell tumour, NOS, was favoured with the emphasis that these tumours have an uncertain malignant potential. The large tumour size and associated necrosis, mitotic activity and nuclear pleomorphism raises the possibility of potentially malignant behaviour in this case.

## 4. Conclusion

In conclusion, this rare category of androgen secreting ovarian tumours can have very different clinical manifestations. A clinicopathological correlation is very important as the benign-looking tumours on histomorphology can behave in a clinically malignant manner. Careful immunohistopathological analysis of submitted specimens can be extremely useful in arriving at a definite diagnosis when the classic presentation is absent. Treatment should be individually based on tumour pathological and histological features, surgical staging, and the desire for future fertility. Depending on age and stage, salpingo-oophorectomy with or without hysterectomy and surgical staging is treatment of choice [8].

## Patient anonymity and informed consent

Written informed consent was obtained from the patients for publication of this case report and accompanying images.

## Ethical approval

N/A.

## Funding

N/A.

## Author contribution

**Nishani Jayatunge**: Conceptualization, Writing - original draft; **Timothy Duncan**: Data collection; Writing - review & editing; **Sarah Knapp:** Data Curation; **Nicholas Oligbo:** Resources; **Niruthan Thirunavukkarasu**: Investigation; Data curation; **Jasenka Mazibrada:** Supervision, Writing - review & editing.

## Guarantor

Dr Jasenka Mazibrada.

## Research registration number

Not applicable.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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