Radiology Case Reports 12 (2017) 838–844

Available online at www.sciencedirect.com

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Oncology

Adrenal mass of unusual etiology: Ewing sarcoma in a young man

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ARTICLE INFO

Article history:
Received 9 April 2017
Received in revised form 19 June 2017
Accepted 3 July 2017
Available online

Keywords:
Adrenal gland
Ewing sarcoma
Neuroectodermal tumor

ABSTRACT

Ewing sarcoma and peripheral primitive neuroectodermal tumor belong to the Ewing sarcoma (ES) family of tumors originating from a primitive neural tube. We report a 31-year-old man who was admitted to the urology clinic with complaints of fever, nausea, and dysuria. A right-sided adrenal mass was detected during ultrasonography. The lesion was then evaluated with magnetic resonance imaging, which showed areas of necrosis amid heterogeneous solid areas. Whole body scan with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography and bone scan studies showed pulmonary and osseous metastatic foci. The mass and right kidney were removed by an open approach. An immunohistochemical and molecular workup enabled the diagnosis of ES. The patient also underwent radiotherapy and chemotherapy. The patient remained in fairly good health during the 18-month follow-up period, but showed progression of all metastatic foci and died 26 months after treatment. In conclusion, adrenal ES should be included in the differential diagnosis of nonfunctional adrenal lesions despite its rare occurrence.

Introduction

Ewing sarcoma (ES), peripheral primitive neuroectodermal tumor (PNET), extraskeletal ES, and Askin tumor (thoracopulmonary PNET) constitute a group of tumors collectively called Ewing sarcoma family of tumors (ESFT), which originates from a primitive neural tube [1,2]. Ewing sarcoma and peripheral primitive neuroectodermal tumor (ES/PNET) comprises a group of small, round, and blue cell tumors that are related to each other on a molecular and immunopathologic basis. These tumors usually occur in long or flat bones, in the chest wall, in soft tissues, and, to a lesser extent, in paravertebral locations and along the genitourinary tract, including

Competing Interests: The authors declare that they have no conflict of interest.

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https://doi.org/10.1016/j.radcr.2017.07.002

the kidney, the urinary bladder, and the vagina [2–4]. Involvement of the adrenal gland in ES/PNET is an extremely rare occurrence. To our knowledge, only about 19 cases of primary adrenal involvement have been reported in the literature, with most cases in the adolescent population and in young adults [5]. Despite its rarity, ES/PNET should be included in the differential diagnosis of an adrenal mass among the more common entities such as adenoma, pheochromocytoma, neuroblastoma, and adrenal cancer. Additionally, ES/PNET must be distinguished from renal tumors [5]. Adrenal ES/PNET is usually managed with surgical intervention followed by chemoradiotherapy, called multimodal treatment; however, no established guidelines exist so far regarding the optimal treatment [6].

In the present study, we report an adrenal ES/PNET case of a young man with distant metastases who was treated with multimodal treatment with some progression in the metastases during an 18-month follow-up and died 26 months after treatment. Literature in English pertinent to the cases of primary adrenal ES/PNET presented so far has also been reviewed at the end.

Case report

In this case report, we present the case of a 31-year-old man who was referred to the urology clinic because of complaints of mild dysuria and fever reaching 104°F for the last 4 days. The patient also complained of nausea and vomiting since 3-4 months and a nonspecific pain in the right hip. The family history was not remarkable, with no history of tuberculosis or malignancy. Blood tests showed leukocytosis (white blood cell, 21,000/mm^3) with neutrophil predominance (16,900/mm^3). All other hematologic parameters were within normal limits. The physical examination was also normal. The ultrasonographic examination revealed a heterogeneous solid right adrenal mass measuring $20 \times 12 \times 14$ cm. Testing for the functionality of the adrenal mass showed no excess metabolites both in blood and urine, including vanillylmandelic acid, 24-hour cortisol, catecholamines, aldosterone, and dehydroepiandrosterone sulfate. Magnetic resonance imaging was then performed to further delineate the mass, which showed areas of increased intensity on T2-weighted imaging, consistent with necrosis and heterogeneous contrast enhancement of solid areas on T1-weighted imaging. Diffusion-weighted imaging with a b value of 1000 showed heterogeneous areas of enhancement with a corresponding decrease in apparent diffusion coefficient values, which was consistent with the restricted diffusion, and areas that were hyperintense on both diffusion-weighted imaging and apparent diffusion coefficient, suggesting necrosis (Fig. 1). Whole-body scan with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (F18-FDG-PET/CT) showed areas of increased metabolic activity in the lingular segment of the left lung, and a bone scan with single-photon emission computed tomography (CT) showed suspicious foci on the S1 vertebra and on the left femoral head, suggestive of lytic-sclerotic metastases.

The patient's fever and nausea were likely attributed to the malignancy.

An open right nephrectomy, along with adrenalectomy, was performed. The patient was discharged on postoperative day 3 without immediate complications.

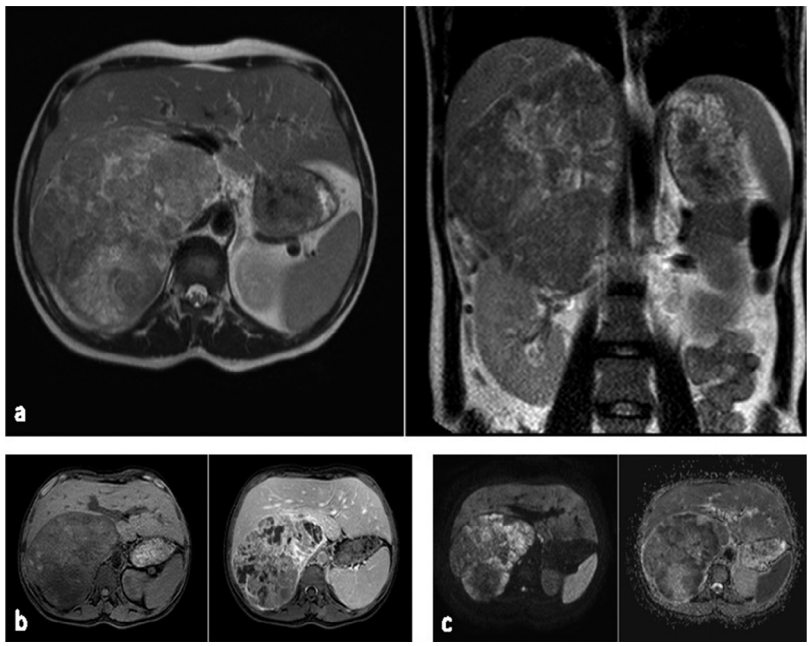

Fig. 1 – (A) Axial and coronal T2-weighted images show a large right adrenal mass partially displacing the liver. The mass has heterogeneous areas of low and high signal intensities, suggestive of solid and necrotic areas. (B) Precontrast and postcontrast fat-saturated T1-weighted images show heterogeneous areas of contrast enhancement. (C) Diffusion-weighted imaging shows that the solid areas restrict diffusion, consistent with high cellularity. The corresponding apparent diffusion coefficient image shows these areas as hypointense, confirming the restriction of diffusion.

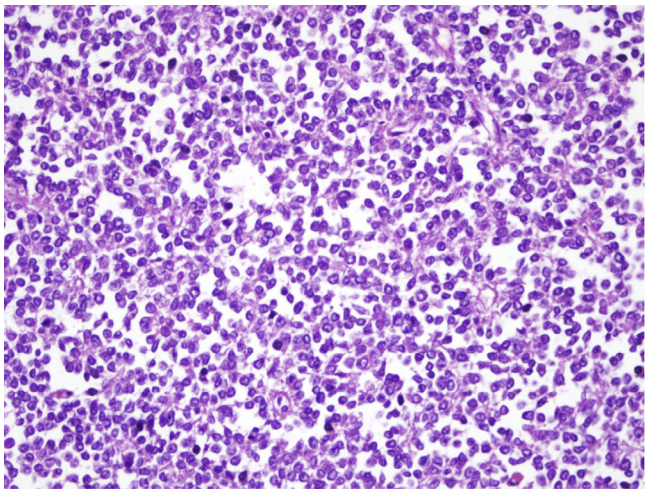

Fig. 2 – Sheets of small round tumor cells with vesicular nuclei and scant cytoplasm arranged in irregular masses and forming rosettes (hematoxylin and eosin stain, ×400).

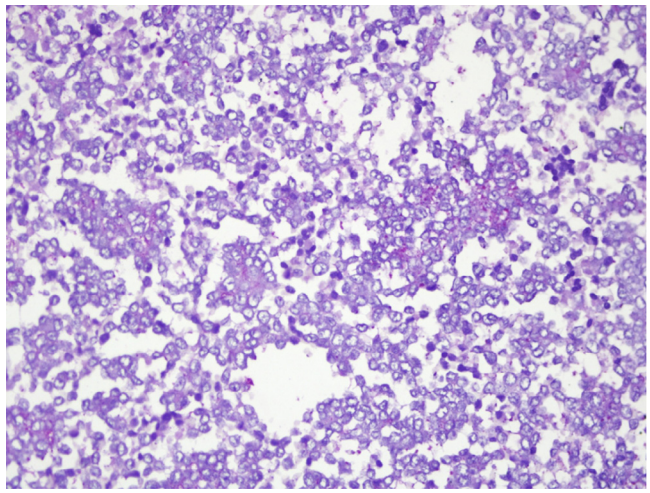

Fig. 4 – Positive staining of tumor cells using periodic acid-Schiff caused by the presence of intracytoplasmic glycogen (×400).

The gross pathologic specimen measuring 20 × 14 × 10 cm weighed 2000 g with an intact capsule, which suggested no intraoperative spillage into the abdominal cavity.

A 20%-30% necrosis was present within the specimen. There was no sign of renal invasion. Lymphovascular invasion was present and 1 aortocaval lymph node out of 13 that were removed during operation showed metastatic involvement.

Microscopic features of the tumor showed homogenous, small, round, and blue cells (Fig. 2).

In the immunohistochemical study, there was positive staining for synaptophysin and cluster of differentiation 99 (CD99) and negative staining for cytokeratin 7, chromogranin A, pancytokeratin, inhibin, calretinin, antibody to melan-A, low–molecular weight cytokeratin, thyroid transcription factor-1, neuron-specific enolase, FLI1, and desmin (Fig. 3). On histochemical examination, cytoplasms of tumor cells stained positive with periodic acid-Schiff, showing intracellular glycogen, which is typical for ES, and thus stained negatively with periodic acid-Schiff diastase (Fig. 4).

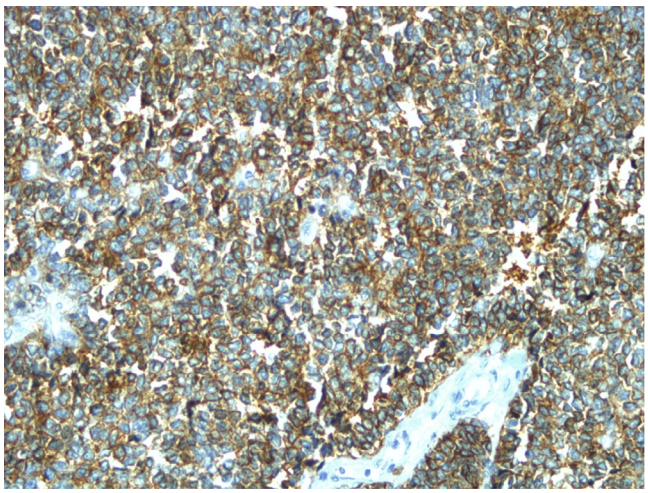

Fig. 3 – Membranous cluster of differentiation 99 expression of tumor cells (×400).

Fluorescence in situ hybridization using dual-color break-apart probes showed the presence of translocation of the Ewing sarcoma breakpoint region 1 (*EWSR1*) gene at chromosome 22q12, and the reverse transcriptase polymerase chain reaction studies were positive for the *EWSR1-FLI1* fusion transcript, all of which strongly suggested the diagnosis of ES/PNET in the adrenal gland [5,7,8].

Although there are no optimal treatment guidelines published, the multimodal treatment with surgery and chemotherapy, sometimes coupled with radiotherapy, is widely recognized as an effective method of treatment [1,4–6,9]. After an open-approach nephrectomy and adrenalectomy, our patient was also put on postoperative chemotherapy regimen consisting of vincristine, doxorubicin, cyclophosphamide, and temozolomide. The patient also underwent 10 courses of local radiotherapy. Although the patient remained in fairly good health during the 18-month follow-up period, he showed progression of all metastatic foci and died 26 months after the treatment. The patient gave consent for the use of his medical data in this report.

Discussion

PNET and ES are malignant neoplasms, possibly of neuroectodermal origin. Because of their common cytogenetic and immunohistochemical elements, these malignant neoplasms are included in ESFT [1]. These malignant neoplasms characteristically have a nonrandom translocation of the *EWSR1* gene on chromosome 22q12 with resultant chimeric genes including t(11;22)(q24;q12) and an *EWSR1-FLI1* chimeric gene. These genes express the MIC2 gene product CD99, a cell surface glycoprotein and a transcription protein, leading to uncontrolled cellular proliferation and tumorigenesis. Some studies suggest that chimeric gene structures correlate with patients' prognosis. In about 5%-10% of the cases, there is a second type of

translocation involving t(21;22)(q22;q12), leading to the *EWS-ERG* fusion gene [3,6,10,11].

Histologically, in our case, there were small, round, and malignant cells, which can be found in neuroblastoma, rhabdomyosarcoma, Wilms tumor, desmoplastic small round-cell tumor, lymphoma, solitary fibrous tumor, poorly differentiated neuroendocrine carcinoma, poorly differentiated synovial sarcoma, extraskeletal mesenchymal chondrosarcoma, melanoma, and ESFT [2]. Differentiation of ES/PNET from a neuroblastoma, based on CD99 staining of the former, becomes important, particularly in the pediatric population, as the treatment and prognosis of these 2 tumors are entirely different. Immunostaining for membranous CD99 is a useful marker for ES/PNET. CD99 staining also rules out neuroblastoma, one of the main differentials in the pediatric age group [7]. However, membranous CD99 is not specific to ES/PNET and can be also found in certain small round-cell tumors [4,9,12,13]. Although *EWSR1* translocation indicates the presence of ES/PNET, desmoplastic small round-cell tumors or myxoid liposarcoma can also express this type of translocation, whereas <1% of ES/PNET have no translocation at all. Our case exhibited both *EWSR1-FLI1* translocation and positive staining for CD99, both of which strongly advocate the diagnosis of ES/PNET [1–7,9,10,12,13].

Increased urinary vanillylmandelic acid and homovanillic acid favor neuroblastoma, which was within normal limits in our patient [14]. Certain immunohistochemical and cytogenetical features may help make the diagnosis of small round-cell tumors or distinguish 1 entity from others. Staining for CD56 and NB84 and marked cytoplasmic Bcl-2 positivity suggest neuroblastoma, whereas staining for muscle-specific proteins (eg, myogenin, desmin, and actin) favors rhabdomyosarcoma, especially the alveolar type. Genetic markers, such as the *PAX3-FKHR* fusion gene expression can also aid in the diagnosis of alveolar rhabdomyosarcoma [15–17]. Wilms' tumor stains usually with CD56, CD57, CK22, CK18, EMA, and SMA, and in most cases, there is no genetic mutation except that, in 20%-30% of the cases, mutations of the *WT1* gene on chromosome 11p13 and inactivation of a gene on the X chromosome, WTX can be encountered [18,19]. Immunostaining for desmin, positive staining for antibody against WT1 protein, and demonstration of a *EWS-WT1* gene fusion suggest desmoplastic small round-cell tumors [20,21]. Immunostaining by reactivity of lymphoma cells to lymphoid markers and negativity to epithelial, neuroendocrine, and myogenic markers favor the diagnosis of lymphoma [20]. For the diagnosis of solitary fibrous tumors, immunostaining for CD34 and STAT6 can be helpful, and demonstration of fusions of the 2 genes, NGFI-A binding protein 2 (*NAB2*) and STAT6, located at chromosomal region 12q13, further confirms the diagnosis [22,23]. Diagnosis of poorly differentiated neuroendocrine carcinoma can be suggested by immunostaining with CD56, synaptophysin, and chromogranin, whereas poorly differentiated synovial sarcoma can be diagnosed by demonstration of t(X;18)(p11.2,q11.2) translocation and reactivity for epithelial membrane antigen, cytokeratin AE1/AE3, and E-cadherin [24,25]. Extraskeletal mesenchymal chondrosarcoma has inconsistent genetic markers but stains strongly positive for S-100, CD99, and vimentin [26]. Finally, melanoma has a high sensitivity for S-100 staining, and Ki67 staining helps differentiate benign lesions from malignant lesions. Demonstration of mutations in the *MC1R* gene and of the *MDM2 SNP309* gene may further help confirm the diagnosis [27,28].

ES/PNET is a malignancy of childhood and adolescence with a slight male predominance. ES/PNET typically involves the axial skeleton and extremities and, to a lesser extent, soft tissues and other solid organs [1]. As in all ESFT, ES/PNET exhibits rapid metastatic progression and may sometimes invade the renal vein or the inferior vena cava [1,2]. In our case, pulmonary and osseous metastatic foci were present at the initial presentation.

With advancing diagnostic methods, unusual primary sites for ES/PNET other than in the bone and soft tissues are also encountered. Our patient had no obvious evidence of a primary tumor site other than the adrenal gland. Therefore, combined with the immunohistological and molecular findings, this patient represents one of the rare cases of primary adrenal ES/PNET, adding to the already reported 19 cases. Most of these 19 cases are older than 17 years, with no gender and laterality predilection. Twelve cases reported so far have been treated with the multimodal treatment of surgery and chemoradiotherapy. Two patients underwent chemotherapy before surgery, to which they responded. In 1 suicidal patient, the diagnosis was incidental at autopsy, and in the remaining 5 patients, the treatment regimen could not be assessed. In 8 patients, metastatic foci were present at the initial diagnosis, and 5 of these patients died during an 11-month follow-up, suggesting that the prognosis is likely affected by the presence of metastases. In 4 patients, venous thrombus was detected and was removed by thrombectomy. As of 2013, 3 patients showed no evidence of disease on a mean 12-month follow-up, whereas 4 patients were alive with disease (Table 1) [1–4,6,9,14,29–32]. As a summary, according to original reports, 6 of these 19 cases died—1 was a suicidal patient, and 5 had metastases. We could not obtain information on the current status of the remaining cases.

Although the present case remained in fairly good health during the 18-month follow-up period, the patient showed progression of all metastatic foci and died 26 months after treatment.

To date, there is no general consensus established about the optimal chemoradiotherapy and multimodal treatment for patients with adrenal ES, possibly because of the rare occurrence of the entity [6]. There are, however, guidelines for the workup and management of incidentally found adrenal lesions, to which we adhere in our institution. The differential diagnosis of an adrenal mass consists of adenomas, which are mostly nonfunctional; adrenocortical carcinomas, which peak around the first and fourth decades; and adrenomedullary tumors such as pheochromocytoma and neuroblastoma, which are usually common in the pediatric age group and are associated with increased catecholamines [2,5,6]. Because of its rare occurrence, we did not initially entertain the diagnosis of ES/PNET.

The diagnosis of adrenal lesions can be readily made with CT and magnetic resonance imaging. Although there are established criteria in these modalities to help in differentiating benign lesions from malignant lesions, a specific diagnosis of an adrenal lesion, particularly that of an ES/PNET, cannot be made with either CT or magnetic resonance imaging.

Table 1 – Reported cases of all age groups with adrenal ES/PNET in the English language literature.

Age (y)	Gender	Symptoms	Side	Metastasis	EWSRI	Operation	Chemotherapy	Radiotherapy (cGy)	Reference
1st decade									
4*[1]	Male	NA	NA	Lung	—	Total resection	V, Ac, AC, P, T	Lung, 2520/adrenal, 3600	[16]
7	Male	NA	NA	Lung, bone	—	Total resection	P, C, A, T, E, V, D	Bone,[2] 3500	[16]
2nd decade									
11	Male	RUQ pain	Right	Peritoneal seeding	PCR	Partial resection	Pd, C, V, A, M	+	[2]
17*	Female	NA	NA	Lung, liver, nodes	—	Biopsy	P, C, A, T, E	Adrenal, 2800	[16]
17	Female	LUQ pain	Left	—	FISH	Total resection	VAC/IE	Abdomen, 3600/focal, 1980	[6]
17	Male	RUQ pain	Right	Lung	FISH	Not operated	V, D, C/I, E	—	[1]
17	Female	Right flank pain	Right	—	FISH	Total resection with spillage	V, A, C/I, E	Whole abdomen	[4]
20	Female	NA	NA	NA	—	NA	NA	NA	[17]
3rd decade									
21	Female	NA	Left	Liver	—	Biopsy	—	—	[18]
22	Male	NA	Left	Thrombus	—	Total resection	V, A, C/I, E	—	[18]
24	Female	Flank pain	NA	NA	NA	NA	NA	NA	[17]
24	Female	NA	Right	Nodes	—	Total resection	V, A, C/I, E	—	[18]
25	Female	Abdominal pain	Left	Thrombus	NA	NA	NA	NA	[17]
26	Male	NA	Right	—	—	—	—	—	[3]
26	Female	LUQ pain	Left	Thrombus	FISH	Total resection, thrombectomy	Cx, A, V/I, E	+	[10]
26	Female	Left flank pain	Left	Thrombus	—	Wide excision with thrombectomy	+	+	[14]
28	Female	Palpable mass	Right	Lung	PCR	Adrenalectomy	V, A, C/I, E	—	[19]
>3rd decade									
31	Male	Fever, nausea	Right	Lung, bone	FISH	Total resection	V, D, C, Tm[3]	Local	This study
57	NA	NA	NA	NA	NA	NA	NA	NA	[8]
63	Male	Hematuria, PSA+++	Left	—	PCR	Adrenalectomy	NA	+	[8]

*Confirmed by neither cluster of differentiation 99 (CD99) immunostaining nor *EWSR1* gene translocation.
[1]With a diagnostic suspicion of peripheral primitive neuroectodermal tumor vs neuroblastoma.
[2]Radiation only to the metastatic site.
[3]Alternating every 2 weeks: ifosfamide and etoposide.
A, adriamycin; AC, adriamycin and cyclophosphamide; Ac, actinomycin-D; C, cylophosphomide; Cx, cytoxan; D, dacarbazine; E, etoposide; ES/PNET, Ewing sarcoma and peripheral primitive neuroectodermal tumor; *EWSR1*, Ewing sarcoma breakpoint region 1; FISH, fluorescence in situ hybridization; I, ifosfamide; LUQ, left upper quadrant; M, methotrexate; NA, not assessed; P, platinum; PCR, polymerase chain reaction; Pd, prednisolone; PSA, prostate-specific antigen; RUQ, right upper quadrant; T, teniposide; Tm, temozolamide; V, vincristine.

F18-FDG-PET/CT is widely used to detect and, more importantly, to stage ES, as well as to evaluate the response after therapy, particularly in pediatric patients. When combined with CT (F18-FDG-PET/CT), FDG-PET is more accurate for small lesions [6,33,34]. In our case, the pulmonary and osseous metastatic foci have been followed up by F18-FDG-PET/CT for 18 months. In patients without obvious metastases, conventional CT is used in some centers in the follow-up period.

Traditionally, adrenal malignancies have been managed with radical open surgeries. Our patient has also been operated on with a radical open approach, with no postoperative complications. However, in recent years, laparoscopic adrenalectomy is more widely used because of its inherent safety in uncomplicated adrenal lesions, including adrenal malignancies [6].

Adrenal ES is an extremely rare occurrence and, thus, is usually not included in the usual differential diagnosis list for an adrenal lesion. Despite its rarity, adrenal ES should remain in the differential diagnosis among the more commonly encountered entities. Immunohistochemical and molecular studies are necessary to make a definitive diagnosis. Currently, there are no established therapeutic strategies for adrenal ES, although a multimodal treatment is widely used, as in osseous ES. However, long-term data are still lacking regarding optimal therapy, and further studies and data are needed.

In conclusion, here we report a case of adrenal ES/PNET, which adds to the limited number of documented cases in literature. We are of the opinion that adrenal ES should be included in the differential diagnosis list of adrenal masses despite its rare occurrence.

Acknowledgment

The authors would like to thank Enago (www.enago.com) for the English language review.

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