Juvenile granulosa cell tumor of the ovary presenting as isosexual precocious puberty: A case report*

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ABSTRACT

Isosexual precocious puberty is rare and a thorough investigation must be done in order to identify the cause of the precocity. This paper presents the case of a 4 year-old girl who was brought to the emergency room due to vaginal bleeding associated with onset of secondary sexual characteristics. Estradiol and anti-mullerian hormone levels were elevated. Abdominal ultrasound revealed an abdominopelvic mass probably an ovarian new growth with benign sonologic features. Computer tomography of the brain with contrast showed normal findings. Elective surgery was planned after correction of the anemia and other causes of precocious puberty were excluded. She underwent an exploratory laparotomy and left salpingooophorectomy with frozen section. Final histopathology report showed juvenile granulosa cell tumor of the left ovary.

Keywords: Juvenile granulosa cell tumor, precocious puberty, ovarian tumor, pediatric endocrinology

INTRODUCTION

Isosexual precocious puberty in girls is rare, with an overall incidence estimated to be 1:5,000 to 1:10,000 with a female to male ratio of approximately 10:1. Most are idiopathic in origin[1]. Several differential diagnoses must be considered in evaluating the cause of precocity in girls. We report a case of isosexual precocity in a 4 year-old girl secondary to a juvenile granulosa cell tumor (GCT) of the ovary (JGCTO). This case report aims to discuss the causes of precocious puberty in a young female, to present the diagnostic approach in evaluating isosexual precocious puberty in a young female and to discuss the management and prognosis of isosexual precocious puberty secondary to juvenile granulosa cell tumor of the ovary.

CASE REPORT

This is the case of a 4 year-old girl who was brought to our institution due to vaginal bleeding. The patient's condition started two months prior to admission when she complained of vague abdominal pain, characterized as intermittent and diffuse, with no relation to feeding. She was brought to a local health center where she was diagnosed with intestinal parasitism. Anti-parasitic medication was taked with no relief of symptom. Three weeks prior to admission, the patient had vaginal bleeding soaking one panty liner per day associated with intermittent abdominal pain. She was brought to an obstetrician where a transrectal ultrasound revealed an ovarian new growth. The family was advised admission however, they were unable to comply due to financial constraints. Two weeks prior to admission, there was increase in the amount of vaginal bleeding, which soaked 7-8 pads per day progressing to 4-5 baby diapers per day associated with generalized pallor. The patient was brought to a local hospital where she was admitted. A repeat transrectal ultrasound was done which revealed an ovarian new growth. The family then decided to transfer the patient to our institution.

On the review of systems, the patient had weight loss and pallor. She had no history of seizures, headache, vomiting and visual disturbances. Developmentally, there was no delay in the patient and is at par with age.

On admission at our institution, the patient was pale, awake, active and not in respiratory distress. Blood pressure was 80/50 mmHg, heart rate was 130, respiratory rate was 20, temperature was 37.1^0C and O_2 saturation was 99 %. She had a breast Tanner stage II (presence breast bud) (Figure 1). Her abdomen was protuberant with a 12 x 12 cm predominantly cystic, movable and non-tender abdominopelvic mass. Genital examination revealed Tanner stage I (presence of prepubertal pubic hair) (Figure 2). Digital rectal examination revealed tightsphincter tone with no intraluminal or cul de sac mass. Volume resuscitation with plain lactated ringers' solution was done which stabilized her blood pressure at 110/70 mmHg. Baseline laboratory examinations (Table 1) were requested which revealed anemia, elevated serum estradiol and anti-mullerian hormone and bone aging compatible with her chronologic age. Transabdominal/transperineal ultrasound revealed a multiloculated cystic abdominopelvic mass (Figure 3). Cranial tomography scan was unremarkable. The admitting impression was precocious puberty secondary to ovarian new growth and anemia secondary

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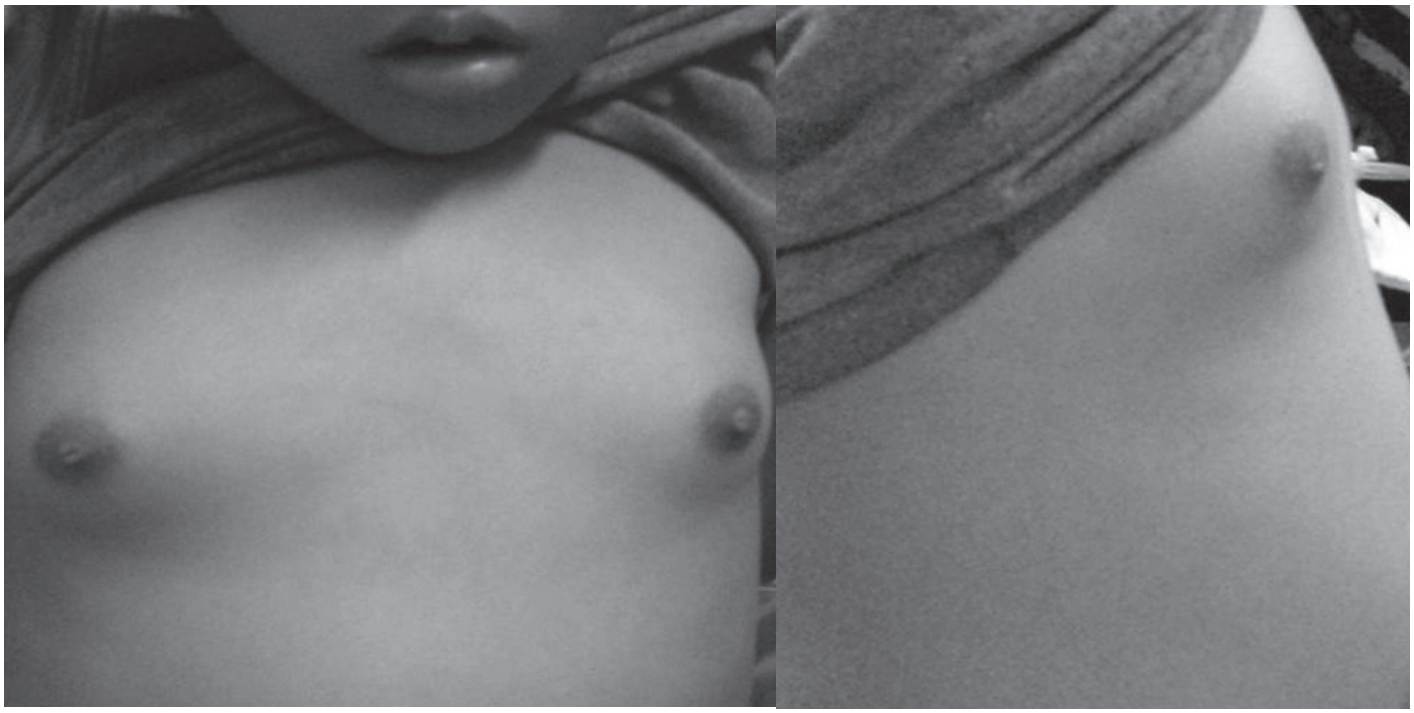

Figure 1. Photo showing presence of breast bud (Tanner stage II) in the index patient.

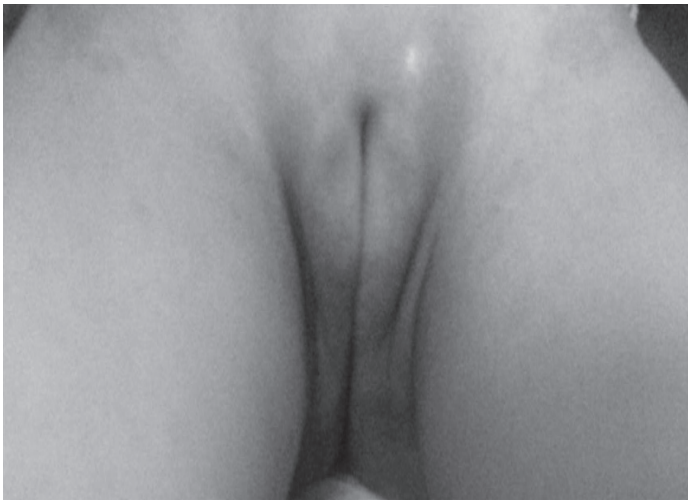

Figure 2. Photo showing presence of prepubertal pubic hair (Tanner stage I) in the index patient.

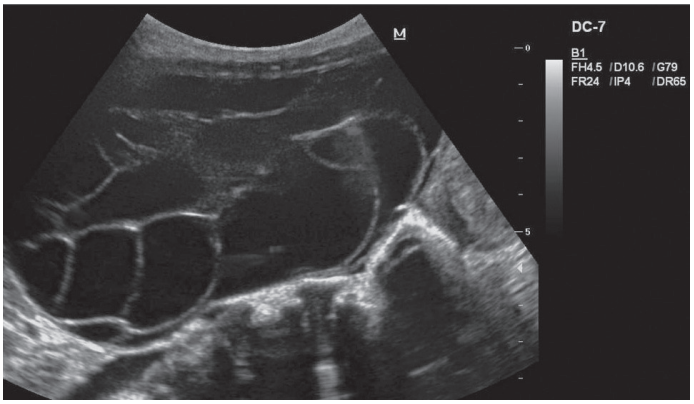

Figure 3. Transabdominal/ Transperineal ultrasound showing a multiloculated and multiseptated abdominopelvic mass.

to chronic blood loss. After correction of the anemia and pediatric clearance was obtained, the patient underwent exploratory laparotomy, unilateral salpingooophorectomy, frozen section, infracolic omentectomy and palpation of lymph nodes. Intraoperatively, there was 200 cc of serous ascites. The left ovary was converted to a 14.5 x 12.5 x 6 cm multiloculated, multiseptated cystic mass serous fluid within. On cut section, there were no necrosis, solid areas or hemorrhages noted. The capsule and septum were smooth and measured 0.2 cm (Figure 4). The rest of the abdominopelvic organs appeared grossly normal. Frozen section of the left ovary favored a sex cord stromal tumor. Intraoperative stage was IA. The patient tolerated the surgical procedure and had an unremarkable postoperative course. She was discharged stable. Final histopathologic report revealed juvenile granulosa cell tumor of the left ovary. Patient was referred to Pediatric Oncology and the plan was to continue surveillance for the next three years by clinical assessment and measurement of serum markers to detect possible recurrence. One month after the operation, the patient was seen at the outpatient department with no recurrence of vaginal bleeding. Examination of the breast and genital area revealed no regression of the breast bud and pubic hair, respectively. Repeat estradiol during this time revealed normal level.

Table 1. Pertinent Laboratory Tests and Results.

Diagnostic	Result	Comments
Complete blood count	Hemoglobin: 58 Hematocrit 0.208	
FT4	17.9	Normal range
Thyrotropin releasing hormone	1.7	Normal range
Alpa feto protein	0.476 IU/ml	Low
CA 125	62.2 U/ml	Elevated
CA 19-9	1.4 U/ml	Low
Estradiol	392.7 pg/ml	Elevated
Anti- mullerian hormone	8.98 ng/ml	Elevated
Xray of the wrist	No significant diffrence in between bone age and chronologic age	
Cranial CT scan	Unremarkable contrast enhanced CT of the brain	
Transabdominal/ transperineal ultrasound	Abdominopelvic mass considering an ovarian new growth with benign features (sassone= 4; lerner= 1; IOTA: multiloculated, color score of 1); normal uterus; endometrium compatible with secretory phase.	

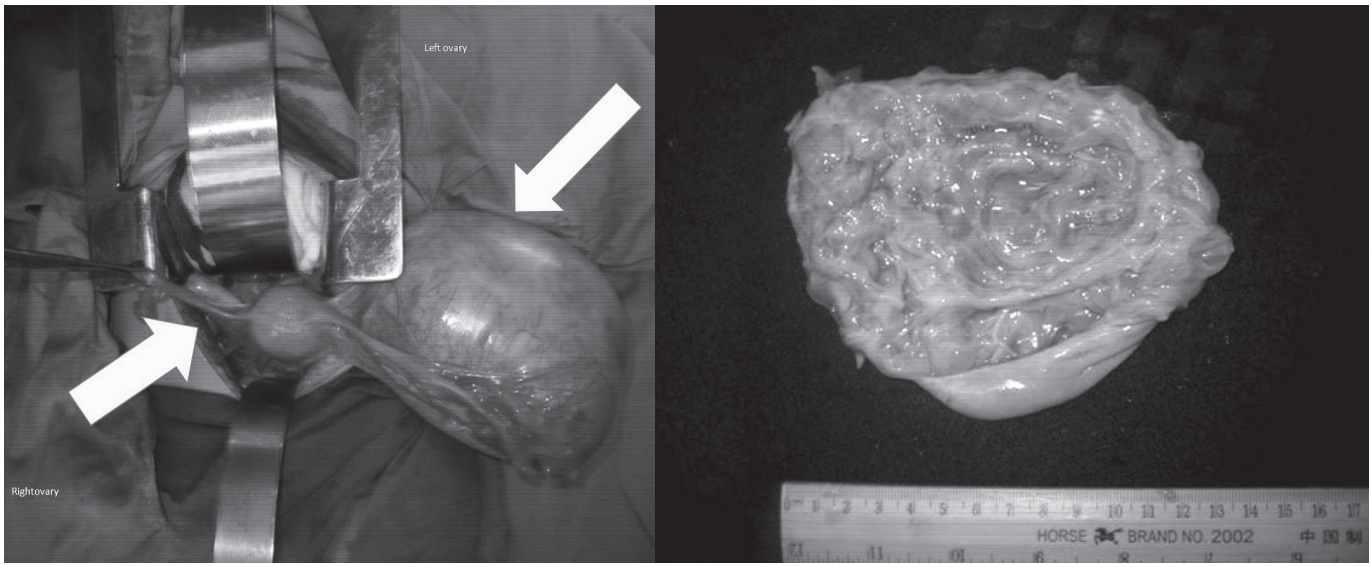

Figure 4. Intraoperative findings.Left photo shows the left ovary converted to a 14.5 x 12.5 x 6 cm cystic mass. Right photo shows the cut section of the left ovary revealing a multiloculated, multiseptated mass with no areas of necrosis and hemorrhage.

The plan was to continue monitoring the patient for possible recurrence but she was lost to follow up.

DISCUSSION

Precocious puberty refers to the appearance of physical and hormonal signs of pubertal development at an earlier age than is considered normal. For many years, puberty was considered precocious in girls younger than 8 years and for boys, onset of puberty before age 9 years.[2]

Precocious puberty can be divided into 2 distinct categories. The first category is gonadotropin-dependent precocious puberty (central precocious puberty), which

involves the premature activation of the hypothalamic-pituitary-gonadal (HPG) axis. In central precocious pubetry, onset of puberty is caused by the secretion of high-amplitude pulses of gonadotropin-releasing hormone (GnRH) by the hypothalamus. Causes include hypothalamic tumors, acquired CNS injury (infection, surgery, trauma, radiation therapy, abscess), congenital anomalies or can be idiopathic.[3]

The second category is gonadotropin-independent precocious puberty (peripheral precocious puberty), in which the presence of sex steroids is independent of pituitary gonadotropin release. Causes of peripheral precocious puberty include gonadal and adrenal tumors; tumors that secrete human chorionic gonadotropin (HCG); McCune-Albright syndrome (MAS) and exposure to exogenous sex steroid hormones.[3]

Determining the etiology of precocity is of utmost importance since the cause may impose a life-threatening condition that warrants immediate intervention. Initial evaluation of children with early development of secondary sex characteristics begins with a thorough history and physical examination. Pertinent points in the history include the age of onset, sequence and progression of the pubertal changes, the timing of onset of puberty of the siblings, presence of neurologic symptoms, exposure to exogenous steroids in food or drugs, history of adoption or even sexual abuse. By history alone, the cause of precocity may already be presumed. Discordant pubertal development (vaginal bleeding within 1 year of breast development) is suggestive of hyperestrogenic state secondary to either McCune Albright syndrome, hypothyroidism or ovarian cysts.[4] Presence of neurologic symptoms such as headache, vomiting or visual problems may indicate presence of an intracranial mass which may point to a probable central cause of the precocity. Review of the patient's food intake and drug usage may reveal exogenous steroid exposure which is a peripheral cause of precocity. Finally, history of adoption from developing countries to a more affluent nations has also been observed in central precocious puberty.[1] The probable explanation to this occurrence is the increase in the body mass index of nutritionally deprived children with resultant increase in the level of sex steroids from adipose tissue.

Physical examination findings of interest include height and weight measurements, body mass index, examination of the breast, skin and abdomen, pubertal Tanner staging (Table 2), neurological examination and any signs of virilization. Based on physical findings, the cause of precocity can also be deduced. Rapid growth and advanced bone age is seen in both central and peripheral precocious puberty except in severe hypothyroidism.[1] Childhood obesity is also associated with the occurrence of central precocious puberty and this is thought to be secondary to the high levels of leptin in obese children which stimulates the release of gonadotropin releasing hormones, luteinizing hormone and follicle stimulating hormone.[5] Examination of the skin may reveal presence of café au lait spots which is a component of McCune Albright syndrome, a peripheral cause of precocity.[6] Pertinent abdominal examination may show the presence of an abdominopelvic mass which may suggest an estrogen secreting ovarian tumor. Absent breast development, presence of axillary and pubic hair on examination of the genitalia with signs of virilization may suggest an adrenal cause of the precocity.[6]

Table 2. Tanner Staging for Girls

Breast	
Tanner I	No glandular tissue; areola follows the skin contour of the chest
Tanner II	Breast bud forms
Tanner III	Breast begins to become more elevated and extends beyond the borders of the areola
Tanner IV	Areola and papilla forms a secondary mound projecting from the contour of the surrounding breast
Tanner V	Breast reaches full adult size
Pubic Hair	
Tanner I	No pubic hair at all
Tanner II	Small amount of long, downy hair on the labia majora
Tanner III	Hair becomes more coarse and curly and extends laterally
Tanner IV	Adult like hair quality, extends across the pubis but sparing the medial thighs
Tanner V	Hair extends to medial surface of thighs

Our index patient, presented with vaginal bleeding and appearance of secondary sexual characteristics. The antenatal, perinatal and neurodevelopmental history were unremarkable. The absence of neurodevelopmental delay on history would already be a clue that the cause of precocity is not secondary to severe hypothyroidism. Furthermore, there was no history of seizures, headache, vomiting and visual disturbances that would point to a probable intracranial mass (central) causing the condition. Based on the sequence and progression of pubertal symptoms, our patient developed breast budding 10 months prior to the onset of vaginal bleeding which based on literature and as previously mentioned suggest a hyperestrogenic state which can be secondary to either McCune Albright

syndrome, hypothyroidism or ovarian mass. On physical examination, however, the patient did not manifests with skin lesions (café au lait spots) or bony deformities making McCune Albright syndrome unlikely. She has Tanner stage II for breast development and Tanner stage I for pubic hair. With breast development and absence of virilizing signs such as hirsutism, clitoromegaly or deepening of voice on examination suggest that the precocity may not be due to an adrenal pathology. Examination of the abdomen showed that it was protuberant with a 12 x 12 cm predominantly cystic, movable and non-tender abdominopelvic mass. From this point, on the basis of history and physical examination, a presumptive diagnosis of the probable cause of the precocity maybe secondary to the palpable abdominopelvic mass.

After a thorough history and physical examination, the evaluation of a child with precocious puberty now proceeds with laboratory evaluation of the different hormones and the utilization of several imaging studies to further narrow done the clinical differential diagnoses (Table 3). GnRH-stimulated gonadotropin level remains the gold standard in differentiating gonadotropin dependent and independent precocious puberty. Pubertal LH levels (>5U/L) and LH to FSH ratio of more than 0.9 are diagnostic of central precocious puberty while a blunted response is pathognomonic of peripheral precocious puberty.[4] Sex hormone levels specifically testosterone >25ng/dl or estradiol >10pg/ml are suggestive of precocious puberty. Furthermore, estradiol levels in the upper end of normal range (75pg/ml) necessitates evaluation to exclude an adrenal or ovarian tumor.[2] If a peripheral cause of precocity is considered evaluation of thyroid hormones will show low free T4 and markedly elevated TSH secondary to severe hypothyroidism. Imaging work-up is based on the clinical presentation of a child with precocious puberty. Magnetic resonance (MR) imaging of the CNS is essential in boys with central precocious puberty where the likelihood of an organic pathology is high. Currently, CNS imaging for girls is recommended if central precocious puberty occurs before age of 6.[4] For girls, pelvic ultrasonography serves two purposes: evaluation for ovarian cyst or tumor as the cause of the precocity as well as evaluation for estrogen-mediated ovarian and uterine maturation.

For our patient, ideally a GnRH-stimulated gonadotropin level should have been done to differentiate central from a peripheral cause however this test is not available in our institution. Furthermore, transabdominal ultrasound revealed an abdominopelvic mass considering an ovarian new growth with benign features (Sassone=4; Lerner= 1; IOTA: multiloculated, color score of 1), which could already be the cause of her precocious puberty. The contrast enhanced CT of the brain also showed unremarkable findings. Radiologic studies, showed that bone age did not differ significantly from her chronologic age. TSH and FT4 levels showed normal values ruling out hypothyroidism. Tumor markers including Ca-125, AFP and Ca19-9 were negative. Serum estradiol and anti-mullerian hormone levels which are markers for granulosa cell tumor were elevated at 8.98 ng/ml and 392 pg/ml respectively. Hence a diagnosis of isosexual precocious puberty secondary to estrogen secreting ovarian tumor was made.

Sex cord–stromal tumors make up the smallest proportion of the general classification of ovarian neoplasms accounting for approximately 8%. Granulosa-theca cell tumors, more commonly known as granulosa cell tumors (GCTs), belong to the sex cord–stromal category and include tumors composed of granulosa cells, theca cells, and fibroblasts in varying degrees and combinations. GCTs account for approximately 2% of all ovarian tumors and can be divided into adult (95%) and juvenile (5%) types based on histologic findings.[7]

Pathologically, GCTs have a soft consistency, are usually solid, and frequently contain cystic areas. They can have several histopathologic patterns, including microfollicular, macrofollicular, trabecular, and insular. The cytologic characteristics of the granulosa cells in juvenile GCTs differ from those of the granulosa cells in adult GCTs. The granulosa cells have abundant cytoplasm, and nuclear grooves are absent. The mitotic rate is high, and Call-Exner bodies are not observed.

Management of granulosa cell tumors begins with surgery for definitive tissue diagnosis, staging, and debulking. The role of chemotherapy or radiation therapy in the treatment of granulosa cell tumors remains uncertain because of the lack of prospective randomized trials supporting their roles as adjuvant agents. Adjuvant chemotherapy with cisplatin-based regimen is needed if the tumor is FIGO stage Ic and IIIc or has a high mitotic rate. The value of postoperative adjuvant therapy for high-risk patients has not been investigated by prospective randomized trials, which are difficult to perform because of the rarity of this tumor. Prognosis depends upon surgical stage at presentation. Fortunately, most patients are diagnosed at stage I, and has a favorable prognosis. Five-year survival rates are 90-95% for FIGO stage I tumors and 25-50% for advanced stages. Because of the propensity of GCT to recur years after initial diagnosis, recurrences occur during the first 3 years after diagnosis, prolonged surveillance with serial physical examination and serum markers such as estradiol, inhibin and anti-mullerian hormone is reasonable.

Our patient underwent exploratory laparotomy, left salpingooophorectomy with an intraoperative assessmentof stage IA. Since our patient is only 4 years old with an early stage disease, a more conservative form

of surgery was done. Postoperative chemotherapy is not warranted for this case since literatures recommend giving cisplatin-based regimen for at least FIGO stage 1c. Long term surveillance by doing serial test for tumor markers and imaging studies specifically transabdominal ultrasound in the first 3 years was advised because of the propensity for the tumor to recur.

The burden of the disease from malignancy in patients with precocious puberty secondary to a malignant ovarian new growth is not only the sole concern of these patients. The early onset of secondary sexual characteristics in patients with precocious puberty makes them vulnerable to sexual assault. Issues on body image, untoward public/ peer treatment, tangential psychological and emotional nurturing causes anxiety and confusion to the patient and the family. Thus proper education, counseling and presence of support group to the child and family members is one of the benchmarks in the management of isosexual precocious puberty.

SUMMARY

This paper presented the case of a 4 year-old girl who presented with vaginal bleeding, breast budding and appearance of pubic hair. Thorough work-up revealed a large abdominopelvic mass, which Surgery was done, which revealed juvenile granulosa cell tumors of the ovary. This condition must be considered in all prepubertal patients presenting with signs of early puberty and a palpable abdominal mass.

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