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Case report

Valproic acid induced aplastic crisis and Stevens-Johnson syndrome in a single pediatric patient

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ABSTRACT

Valproic acid (VPA) is a commonly used antiepileptic drug (AED). Aplastic crisis is defined as acute arrest of hematopoiesis. Stevens-Johnson syndrome (SJS) is a fatal cutaneous adverse drug reaction. We herein report a rare case of aplastic crisis and SJS in a single pediatric patient that were probably caused by VPA. A 2-year-old girl was involved in a car accident. She was diagnosed with skull fractures, cerebral contusions, pulmonary contusions, and fractures of the left iliac bone by computed tomography. VPA was administered as prophylaxis for post-traumatic epilepsy. From day 13, she developed repeated high fevers, and multiple antibiotics were ineffective; she was then transferred to our pediatric intensive care unit. After transfer, she developed liver function impairment, decreased peripheral blood cell counts, and skin damage. After withdrawal of the VPA and administration of prednisone, intravenous immunoglobulin, local skin care, and nutritional support, her body temperature normalized and her hematopoietic function and skin lesions successively resolved. She was transferred out of the pediatric intensive care unit on day 56 and discharged on day 70. At the 6-month follow-up, a blood examination was normal, and repeat computed tomography revealed multiple softening foci of the bilateral brain and less subdural effusion than before. To our knowledge, no report to date has described aplastic crisis and SJS in a single patient. The purpose of this paper is to increase clinicians' knowledge in the treatment of adverse drug reactions (ADRs) and emphasize the importance of standardized application and strict monitoring of VPA in patients with post-traumatic brain trauma.

1. Introduction

Aplastic crisis, also known as acute hematopoietic arrest, is characterized by decreased peripheral blood cell counts (more than two lines) and bone marrow hematopoietic cytometry, which can be fatal because of secondary infection or bleeding. The pathogenic mechanism of aplastic crisis is immune damage to hematopoietic cells [1, 2]. This disease is self-limited, and hematopoietic function can be restored without androgens, immunosuppressants, or stem cell transplantation.

Stevens-Johnson syndrome (SJS) is a drug-induced delayed allergic reaction. It can cause damage to the skin and mucous membranes, is associated with many complications (bacteremia, pneumonia, esophagitis, and others), and has a case fatality rate of up to 10%. If SJS is suspected based on clinical manifestations or pathological examination findings, the suspected drug must be immediately stopped and supportive multidisciplinary treatment implemented [3].

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2. Case report

A 2-year-old girl was involved in a car accident. She was admitted to a local hospital and diagnosed with cerebral contusion, calvarial fracture, pulmonary contusion, and fracture of the left iliac bone as confirmed by computed tomography. She was stabilized by treatment with valproic acid (VPA) and mannitol. From day 13 of her clinical course, she developed repeated high fevers (peak of 39.7 °C). Treated with cefoperazone/sulbactam, ceftriaxone, and azithromycin, but her fever did not improve. On the 18th day of her clinical course, the child developed a mild cough with no sputum production, wheezing, shortness of breath, or cyanosis. She showed normal or negative findings on routine, biochemistry and culture examinations of cerebrospinal fluid; peripheral blood count examinations; and C-reactive protein (CRP) and procalcitonin (PCT) measurements. For further diagnosis and treatment, the child was transferred to our department on the 24th day of her clinical course.

On physical examination, she was irritable and had a Glasgow coma scale score of 10 (E4V2M4). Her bilateral pupils were equally large and reacted sensitively to light. Muscular tension was high in all four limbs. The bilateral Babinski sign was positive. She showed no signs of meningeal irritation. Dark red rashes were present on her face, neck, and trunk; some were desquamative, but no exudation or hemorrhage was present (Figure 1). Her breath sounds were rough, but she had no wheezing or rales. There was no significant abnormal sign of cardiac circulation and abdomen.

We found human metapneumovirus virus in bronchoalveolar lavage fluid by metagenomic next-generation sequencing (mNGS). Microbial cultures of the bronchoalveolar lavage fluid, cerebrospinal fluid, peripheral blood, and urine were negative. A routine peripheral blood examination, (1,3)-β-D-glucan test (G-test), and high-sensitivity CRP measurement were normal, but the PCT concentration was mildly elevated (1.24 ng/mL). Routine cerebrospinal fluid and biochemistry examinations were negative. Routine urine and stool tests were also negative. Her alanine transaminase concentration was 531 U/L (reference range, 7–40 U/L), aspartate transaminase concentration was 255 U/L (reference range, 13–35 U/L), gamma-glutamyl transpeptidase concentration was 158 U/L (reference range, 7–45 U/L), ferritin concentration was 1577.9 ng/mL (reference range, 4.6–204 ng/mL), triglyceride concentration was 1.6 mmol/L (reference range, 0.5–2.3 mmol/L), and fibrinogen concentration was 1.4 g/L (reference range, 2–4 g/L) (Table 1). Further tests ruled out autoimmune diseases, pemphigus, and IgE-mediated allergy (anti-nuclear antibody, anti-centromere antibody, rheumatoid factor, anti-streptolysin O antibody, total/classification of IgE, anti-epidermal basal membrane antibody, and anti-epidermal prickle cell antibody were negative). However, tests revealed a $CD4^{+}/CD8^{+}$ T-cell disorder (2.65; reference range, 1.02–1.94) and low B-cell count (91/μL; reference range, 107–698/μL). The blood concentration of VPA was 39.6 μg/mL (effective range, 50–100 μg/mL) in the first hospital on day 9, was 53.1.μg/mL in our hospital on day 27. The peripheral blood cell counts rapidly decreased from the 27th day: the neutrophil count was 0.04×10^9/L (reference range, 1.8–6.3 $\times 10^9$/L), hemoglobin concentration was 76 g/L (reference range, 110–140 g/L), reticulocyte level was 0.1% (reference range, 0.5%–1.5%), and platelet count was 89×10^9/L (reference range, 125–350 $\times 10^9$/L) (Table 2). Bone marrow morphology showed diminution of hematopoietic cells, infiltration of a few lymphocytes and histiocytes, and no hemophagocytosis. Bone marrow biopsy revealed no fibrosis or malignancy (Figure 2).

Considering the above finding as well as the hematopoietic changes and the possibility skin damage of SJS caused by VPA, the following treatments were implemented: (1) discontinuation of all previous antibiotics and VPA, (2) administration of meropenem to prevent infection secondary to severe granulocyte deficiency, (3) small doses of short-course glucocorticoids with the addition of gamma immunoglobulin, (4) nutritional support in the form of feeding an amino acid formula milk powder to reduce the possibility of protein allergy, and (5) basic skin care in the form of strict bedside isolation, hand hygiene, and attention to skin lesion protection.

The child was transferred out of the pediatric intensive care unit on day 56 of her clinical course. She was discharged from the hospital on day 70 with a normal body temperature and recovered skin lesions, and she got recovery of hematopoietic function (discontinuation of blood transfusion, recovery of peripheral blood cell counts, and normal reticulocytes) (Table 2). At the 6-month follow-up, no abnormalities were seen on routine blood examination, and repeat skull computed tomography showed that the volume of subdural fluid had decreased and that multiple softening foci were present on both sides of the brain.

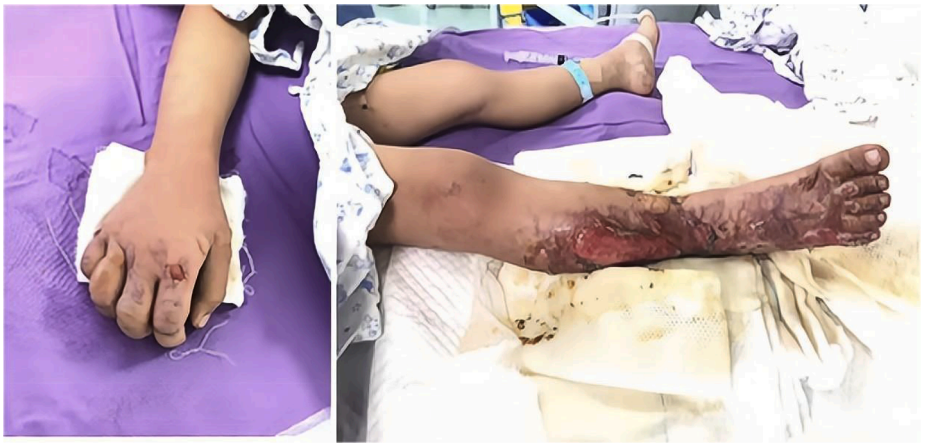

Figure 1. Skin lesion. Erythema with red swelling and epidermal detachment.

Table 1
Liver function impairment.

Day (clinical course)	ALT (U/L)	AST (U/L)	GGT (U/L)	Fbg (g/L)	TG (mmol/L)	Ferritin (ng/ml)	Tpeak (°C)	Clinical events
24							39.1	Transferred to our PICU; Stop all antibiotics
26	531	255	158	1.4	1.6	1577.9	39.4	Administered liver protection drugs
27							38	Stop VPA
31	109	33	103	1.7	2.0	497.8	39.4	
39	29	24	41	2.2			39.5	
58	33	25	10				37.5	
65	28	28	9			620.4	normal	

Table 2
Peripheral blood count, reticulocyte level, C-reactive protein (CRP), procalcitonin (PCT) and clinical events.

Day (clinical course)	WBC (10^9/L)	N_{count} (10^9/L)	N_{level} (%)	L (%)	Hb (g/L)	Ret (%)	Plt (10^9/L)	CRP (mg/L)	PCT (ng/ml)	Tpeak (°C)	Clinical events
24	7.5	3.1	42.1	38.7	101		180	6.8	1.24	39.1	Transferred to our PICU; Stop all antibiotics
26	6.5	1.6	25.5	59.3	76		118	6.5		39.4	Transfused RBCs; Administered meropenem
27	5.8	0.9	16.5	64.7	101		89			38	Stop VPA; Dermatological consultation: drug rashes, local skin care
29	3.4	0.07	2	84.0	88		89	1.5	0.27	38.5	Administered Vitamin B, batilol
31	2.9	0.05	1.7	90.0	103		132	1.3	0.18	39.4	
33	2.8	0.04	1.5	96.6	95		300	7.8		38.7	
38	2.6	0.04	1.4	97.0	87	0.2	361	2.1	0.14	38.2	
39	2.2	0.06	2.7	90.5	78		504	3.4	0.15	39.5	
42	2.8	0.2	7.1	68.2	66	0.1	596			39.2	Transfused RBCs
45	4.9	1.4	28.5	47.5	97		534	1.8	0.14	38.8	Skin damage
49										39	Stop meropenem; Dermatological consultation: IVIG 2.g/kg, prednisone 1 mg/kg*3d, local skin care
53										38.1	Skin improved: scab and epithelial regeneration
56	13.2	5.4	40.5	36.7	74	0.15	484	0.6	0.11	37.7	Discharged from PICU
65	8.1	2.9	36.1	45.7	87		323			normal	Skin lesions resolved
70	7.6	3	39.9	36.5	91	8.9	412			normal	Discharged from hospital

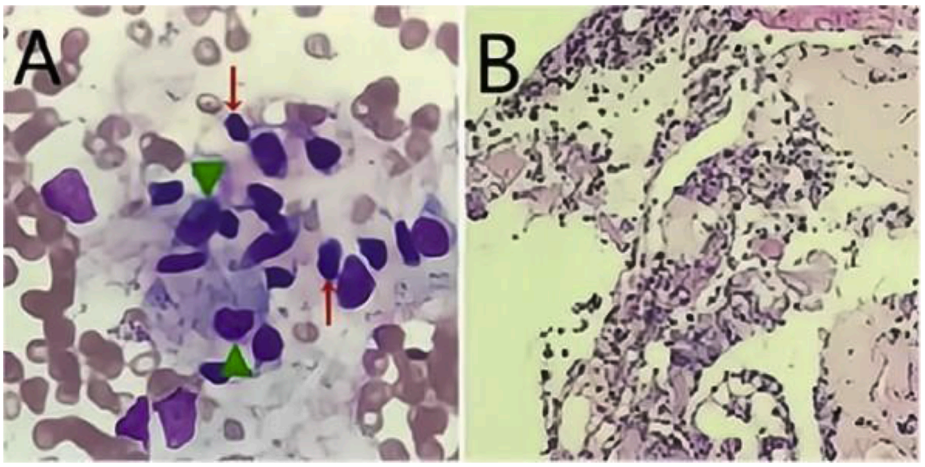

Figure 2. A. Bone marrow morphology. Diminution of hematopoietic cells, infiltrated with a few lymphocytes (red arrow) and histiocytes (green triangle). Wright-Gimsa stain, x1000. B. Bone marrow biopsy. Similar to morphology description. No fibrosis or malignancy. Hematoxylin-Eosin stain, x100.

3. Discussion

The clinical presentation of this case was complex, included recurrent hyperthermia, cytopenia, and impaired liver function. The first step in the differential diagnosis is to check for infection and sepsis. Our protocol to check for infection involves examination of many different specimens and use of multiple diagnostic techniques. In the present case, human metapneumovirus was found only in alveolar lavage fluid by mNGS. Human metapneumovirus, which is common in respiratory tract infections in infants and young children, is similar to human rhinovirus and respiratory syncytial virus; however, it rarely induces a fever for >1 week and a systemic inflammatory response. It does not readily explain the patient's whole course and the involvement of multiple systems. Therefore, we considered that the etiology was likely noninfectious, and we discontinued the antibiotic therapy after transfer.

VPA is a commonly used antiepileptic drug (AED). It is very effective in both adults and children. In this case, the child had been involved in a car accident and was diagnosed with a calvarial fracture, cerebral contusion, and subdural effusion. She was treated with VPA as prophylaxis for post-traumatic epilepsy (PTE). PTE is divided into early-stage PTE (≤1 week) and late-stage PTE (>1 week) depending on the time of its occurrence [4]. Cerebral contusion and calvarial fracture are high-risk factors for PTE [5]. Our patient had indications for prophylaxis for PTE, but the VPA duration of almost 3 weeks was questionable. The guidelines for management of pediatric severe traumatic brain injury (third edition) stated that AEDs are not useful as prophylaxis in patients with late-stage PTE, that AEDs are recommended for high-risk patients for up to 7 days, and that AED use should be monitored with electroencephalography and measurement of the drug concentration in blood [6]. No electroencephalography results were available from the first hospital. The VPA concentration was measured in the first hospital on day 9 and our department right after the referral on day 27, both were within the effective range. After the referral, we discontinued the drugs suspected to be causing her clinical signs (antibiotics and VPA). Soon after the suspension, the impaired hepatic function improved on day 31, the platelet count recovered on day 33, and the neutrophil count normalized on day 45. But it seemed that the immunoreactivity enhanced along with the recovery of the white cell counts, the skin damage appeared on day 45 either (Tables 1 and 2). The possibility of hypersensitivity of VPA could be the genetic etiology. SJS is a drug-induced delayed allergic reaction, as our present case, the total/classification of IgE were negative, however measurements revealed a CD4+/CD8+ T-cell disorder and low B-cell count. Therefore, based on the pathogenology, immunology findings and the clinical manifestation improvements after the withdrawal of VPA, besides the fact that SJS is a known adverse drug reaction by VPA, we concluded that aplastic crsis and SJS was probably caused by VPA in this case according to the Karch-Lasagna classification.

Bone marrow cell morphology and biopsy also played an important role in the differential diagnosis in this case. These tests revealed low numbers of hematopoietic cells with no hemophagocytosis, fibrosis, or malignancy. Hematopoietic cessation indicated aplastic crisis or anemia. As summarized in Table 2, the degree of peripheral blood pancytopenia met the criteria for very severe aplastic anemia; the platelet count recovered early; the pancytopenia and reticulocyte percentage recovered without the use of androgens, immunosuppressive agents, or hematopoietic stem cell transplantation; and no red blood cell infusions were required for 28 days before discharge from the hospital. Therefore, the clinical manifestations met the criteria for aplastic crisis [7, 8].

Aplastic crisis and aplastic anemia share a similar pathogenic mechanism of immune disorder. Hematopoietic stem cells sustain immune injury mediated by $CD8^+$ T cells and cytokines (interferon-γ, tumor necrosis factor-α), aplastic crisis just not severe and permanent as aplastic anemia. Most cases involve infection (*Staphylococcus* [9], human parvovirus B19 [10,11], hepatitis virus [12, 13]) or exposure to non-cytotoxic drugs (isoniazid, thiamazole, interferon, amikacin) [1, 2].

Treatment with prednisone (1 mg/kg per day for 3 days), intravenous immunoglobulin (2 g/kg), and supportive care had a good therapeutic effect in this case. Supportive care is the cornerstone of management for adult and pediatric patients with SJS/toxic epidermal necrolysis. An international multidisciplinary consensus on supportive care in the acute phase of SJS and toxic epidermal necrolysis was published in 2021. It described 14 aspects of care, including immediate discontinuation of suspected drugs, prevention of infection, fluid resuscitation, nutritional support, local skin care, surveillance, and other measures [14].

A systematic review focused on VPA in association with SJS. It enrolled 19 studies (total of 98 cases). In most studies, the occurrence of SJS was followed by VPA treatment with the use of another AED, mainly lamotrigine but also carbamazepine and lorazepam. Pharmacovigilance studies have shown that lamotrigine and carbamazepine are associated with SJS in pediatric patients [15]. In seven case reports, however, drug-induced SJS was triggered by VPA monotherapy. The duration of VPA was <1 month (range of 1–3 weeks) [16]. In our case, VPA was initiated on day 1 and withdrawn on day 27; Fever appeared on day 13 and skin lesions occurred on day 45, along with aplastic crisis. These features are different from the previous literature reports.

4. Conclusion

To our knowledge, this is the first report of aplastic crisis and SJS in a single patient. Adverse drug reactions are various and complicated, and differential diagnosis is important. Clinicians should administer VPA for PTE with strict indications and monitoring and for a specific duration.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no competing interests.

Additional information

No additional information is available for this paper.

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