Case report

Hemophagocytic syndrome associated with varicella

DOI: 10.5377/alerta.v66i1.15443

Cesar Mateo Gavidia Leiva[1*], Ramón David Argueta Sales[2]

1. Ministry of Public Health / Directorate of Epidemiology, San Salvador, El Salvador.
2. Ministry of Public Health / Central Health Region, Santa Tecla, La Libertad, El Salvador.

* Correspondence
cesarmat2015@gmail.com

1. 0000-0002-9351-9359
2. 0000-0001-8174-8114

Síndrome hemofagocítico asociado a varicela

Suggested citation:
Gavidia Leiva CM, Argueta Sales RD. Hemofagocytic syndrome associated with varicella. Alerta. 2023;6(1):12-17. DOI: 10.5377/alerta.v6i1.15443

Received:
December 15, 2022.

Accepted:
January 17, 2023.

Published:
January 30, 2023.

Author contribution:
CMGL[1]: study conception, manuscript design, literature search, data collection, management and analysis, writing, revising and editing. RDAS[2]: literature search, data analysis, writing, revising and editing.

Conflicts of interest:
The authors declare there are no conflicts of interest.

Abstract
Case presentation. A 14-month-old female infant with normal psychomotor development, without comorbidities. With a one-day history of fever of 40 °C, intermittent, accompanied by diarrhea and vomiting. She was taken by her parents to a private clinic without improvement with the indicated medical treatment. Subsequently, she presented clinical deterioration and was taken to a hospital, where she was diagnosed with acute febrile syndrome, diarrhea with mild dehydration, and pharyngitis. On the fourth day of evolution, she started with macules and papules that progressed to vesicles and crusts. In addition, she presented oral intolerance, dyspnea, abdominal distension, coma, and hydroelectrolytic imbalance. **Treatment.** She started treatment with parenteral hydration, antivirals, intravenous steroids, and antihistamines; septic shock with respiratory distress was diagnosed, assisted mechanical ventilation was provided, and she was referred to a tertiary hospital for critical care medicine. Studies reported a 40 % right pleural effusion and hepatomegaly. She continued treatment with antibiotic therapy, parenteral hydration, antivirals, diuretics, antipyretics, and hemoderivatives, presented improvement, and continued therapeutic management. **Outcome.** On day 18 she presented fever and hepatosplenomegaly. Tests reported elevated ferritin, triglycerides, and cytopenia, and was diagnosed with hemophagocytic syndrome that evolved with multisystemic failure and died the following day.

Keywords
Varicella, sepsis, hemophagocytic lymph-histiocytosis, hemophagocytic syndrome.

Resumen
Presentación del caso. Lactante femenina de 14 meses de edad con desarrollo psicomotor normal, sin comórbidos. Con historia de un día de fiebre de 40 °C, intermitente, acompañada de evacuaciones diarreicas y vómitos. Fue llevada por sus padres a una clínica privada sin notar mejoría con el tratamiento médico indicado. Posteriormente, presentó deterioro clínico y fue llevada a un hospital, donde se diagnosticó un síndrome febril agudo, diarrea con deshidratación leve y faringitis. Al cuarto día de evolución inició con máculas y pápulas que progresaron a vesículas y costras. Además, presentó intolerancia a la vía oral, disnea, distensión abdominal, coma y desequilibrio hidroelectrolítico. **Intervención terapéutica.** Inició el tratamiento con hidratación parenteral, antivirales, esteroides endovenosos y antihistamínicos; se diagnosticó shock séptico con compromiso respiratorio, se proporcionó ventilación mecánica asistida y fue referida al hospital de tercer nivel para atención por medicina crítica. Los estudios reportaron un derrame pleural derecho del 40 % y hepatomegalia. Continuó el tratamiento con antibióticoterapia, hidratación parenteral, antivirales, diuréticos, antipiréticos y hemoderivados, presentó mejoría, continuó el manejo terapéutico. **Evolución clínica.** El día 18 presentó fiebre, hepatoesplenomegalia, los exámenes reportaron elevación de ferritina, triglicéridos y citopenia se diagnosticó un síndrome hemofagocítico que evolucionó con una falla multisistémica y falleció al siguiente día.

Palabras clave
Varicela, sepsis, linfohistiocitosis hemofagocítica, síndrome hemofagocítico.

Introduction

Hemophagocytic syndrome is characterized by hyperreactivity of phagocytic cells, which attack hematopoietic cells without regulation of the immune system. It is associated with severe cytopenias due to uncontrolled hemophagocytosis. It can be present in two forms: primary or secondary. Diagnosis is complex, but is suspected when fever, hepatosplenomegaly, cytopenia in at least two cell lines, hypertriglyceridemia or hypofibrinogenemia, and elevated ferritin levels are present[1].

The global incidence is not defined; countries such as the United States of America report an incidence of one per 100 000 inhabitants; in Latin America the incidence rate has not been recorded, but there are reports of patients in whom the syndrome is related to viral infections[2]. Global mortality is 95 % in the absence of treatment, and 40 % with timely treatment. In Latin America, some studies describe a mortality rate of 35 %[2].

Varicella is caused by the varicella zoster virus whose only reservoir is the human being. It causes two diseases: varicella as primary disease and herpes zoster, when there is a reactivation of the virus. The latter is characterized by papular macules with vesicles and crusts, as well as hyporexia and fever. The lesions present in different stages of evolution, initially with a central distribution on the trunk, stomach and thorax, then spreading[3]. The virus is transmitted from person to person, by direct contact with skin lesions, by fomites contaminated by secretion from the lesions and by the airborne route[4]. It rarely occurs in infants because they are protected by the immunity of antibodies in breast milk[5].

Chickenpox is highly contagious. In the United Kingdom, more than 80 % of people have been infected before the age of ten. In the United States of America, mortality in infants and children is approximately seven per 100 000 infants and 1.4 per 100 000 children[6]. The global incidence rate is 2.7 per 100 000 inhabitants, with countries such as Mexico reporting rates of 2.33 per 100 000 inhabitants[7]. The incidence rate reported by Salvadoran studies is 50.8 per 100 000 inhabitants[8]. El Salvador has a vaccination law based on the expanded program of immunization, which does not include vaccines for varicella and hepatitis A[9].

Case presentation

This is a 14-month-old female infant, from the department of La Libertad, of low socioeconomic level, living with her two parents and two siblings nine and 14 years old in a house of mixed construction with two bedrooms. There was no history of allergies, medical or surgical precedents, travel outside the country, or contact with sick people in the last 21 days. The patient was malnourished, with normal psychomotor development and with a complete vaccination schedule for her age, according to the Expanded Program of Immunization[9].

She was initially medicated with acetaminophen 120 mg every six hours. After noticing an exacerbation of the symptoms, the parents decided to consult a private health service. She was brought for consultation with a history of one-day of fever of 40 °C, intermittent; diarrheal, liquid, fetid, yellow color, bowel movements, without glera or blood; and vomiting of gastric contents. On the second day of evolution and with no improvement with the indicated treatment the parents decided to consult a peripheral hospital, where she was diagnosed with acute febrile syndrome, diarrhea with mild dehydration, and pharyngitis; she was admitted into the hospital for study and management. The initial leukogram reported leukocytes of 12 660 and neutrophils of 85 %.

On the third day she continued to be febrile and evolved with oral lesions, a diagnosis of herpetiform stomatitis was made (Figure 1). On the fourth day she presented macules in the thorax region, abdominal distension and difficulty defecating. On the sixth day, the skin lesions were in different stages of evolution; macules, papules, vesicles and

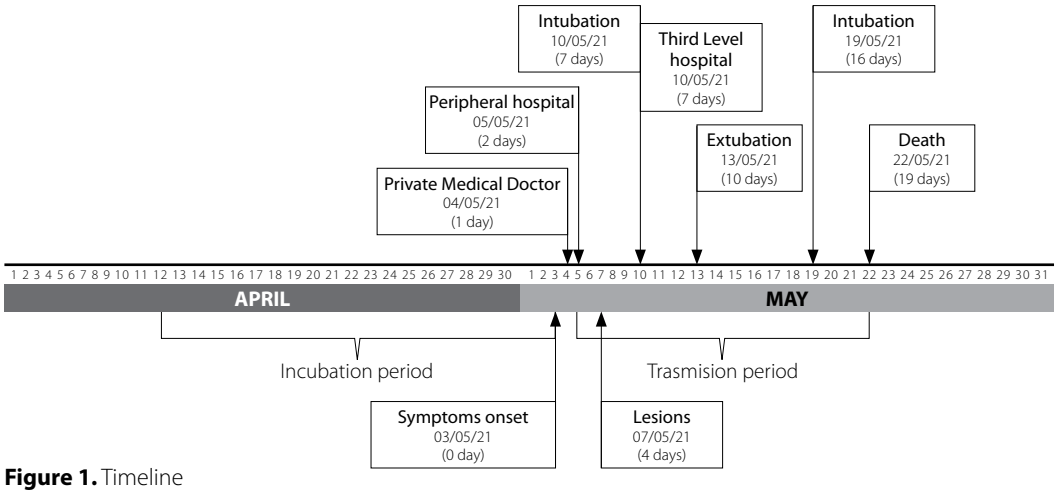

Figure 1. Timeline
Source: Authors´ elaboration

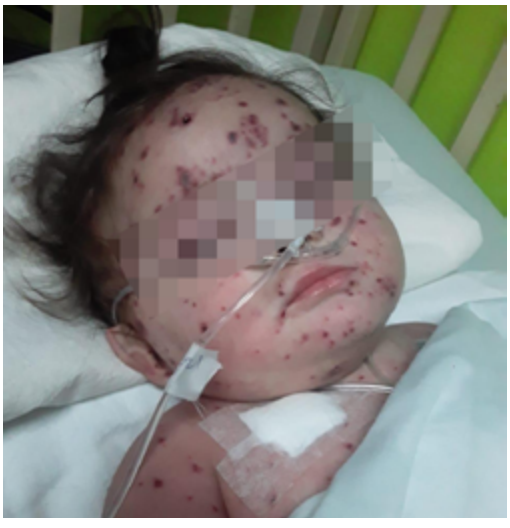

Figure 2. Dermatologic lesions presented
Source: provided by the patient's mother.

crusts (Figure 2). In addition, she presented hydroelectrolyte imbalance, oral intolerance, dyspnea, 85 % oximetry, abdominal distension with Glasgow coma scale of seven points and hydroelectrolyte imbalance.

The patient was treated with 5 % dextrose solution, 20 % sodium chloride, 15 % potassium chloride, 10 % calcium gluconate, ceftriaxone 1 g every 24 hours, methylprednisolone 10 mg every six hours, chlorpheniramine 1 mg every 12 hours.

She was given mechanical ventilation and referred to a tertiary hospital being diagnosed with systemic inflammatory response syndrome, toxic shock, hydroelectrolyte imbalance and intestinal obstruction.

In the emergency unit of the tertiary hospital, the patient was critically ill, pale, under sedative analgesia with mechanical ventilation, with multiple maculopapular lesions on the skin, crusts and vesicles with clear fluid discharge. Blood pressure 102/63 mm/Hg, weak pulse 153 beats per minute, temperature 37.5 °C, weight 12 kg (at the 97th percentile), height 73 cm (at the 50th percentile), head circumference 46 cm. The thorax was hypoventilated at the right lung base with transmitted sounds. The abdomen was globose with absent peristalsis and hepatomegaly.

Anteroposterior chest X-ray and plain abdominal X-ray showed right pleural effusion of 40 %. Abdominal ultrasonography reported hepatomegaly and a splenic cephalocaudal diameter of 7.4 cm (splenomegaly).

Treatment

The patient was admitted to the tertiary hospital in the intensive care unit and was treated with 0.9 % normal saline, 5 % dextrose, 20 % sodium chloride, 25 % potassium chloride, 10 % calcium gluconate, 50 % magnesium sulfate, vancomycin 180 mg every six hours, meropenem 500 mg every eight hours, clindamycin 120 mg every six hours, acyclovir 300 mg every eight hours, hydralazine 2.5 mg every six hours depending on the arterial pressure, clindamycin 120 mg every six hours, acyclovir 300 mg every eight hours, hydralazine 2.5 mg every six hours depending on arterial pressure. In addition, platelets 20 mL every eight hours, packed red blood cells 120 mL every day, dexamethasone 1.5 mg every six hours, human immunoglobulin 10 g in 24 hours, fluconazole 72 mg every day.

Tests showed hemoglobin and leukocytes within normal values, with neutrophilia, fibrinogen 117 g/L, decreased clotting times and elevated liver enzymes (Table 1).

Outcome

On the tenth day of evolution the patient presented clinical improvement, mechanical ventilation was withdrawn, with 100 % oximetry, gag reflex, response to external stimuli, respiratory frequency less than 35 breaths per minute, PaO2/ FiO2 greater than 150-200, PEEP less than or equal to eight cmH2O, systolic blood pressure greater than 90 mmHg and diastolic less than 180 mmHg, temperature less than 38 °C. She started with dyspnea during the ventilator weaning process, continuous positive airway pressure was administered and then a nasal cannula was placed. When dyspnea improved, therapeutic management was continued.

After 18 days of evolution, she presented fever, dyspnea with oximetry of 87 %, hypotension, hepatosplenomegaly, adenopathy, with progressive leukopenia, coagulopathy, respiratory acidosis, cytopenia (hemoglobine 8.8 g/dL and platelets 10 000), ferritin 1500 ng/mL and triglycerides 307 mg/dL[1] (Table 1); which generated a multiorgan failure and died one day later.

Diagnosis

On the eighth day the following diagnoses were determined: acute gastroenteritis with dehydration, varicella, acute liver injury, pneumonia with right pleural effusion and septic shock, and finally, a hemophagocytic syndrome associated with an infection. The diagnosis of varicella was made by clinical and epidemiological criteria.

Discussion

Hemophagocytic syndrome or hemophagocytic lymphohistiocytosis occurs in two

ways: primary when associated with genetic mutations, and secondary when it occurs after autoimmune diseases, neoplasms or infections[10]. Infections related to the appearance of the syndrome are those produced by herpes viruses, human immunodeficiency virus, adenovirus, hepatitis virus, bacteria, fungi and parasites[11]. In the pediatric population, the most common trigger is infections caused by the *herpesviridae* family, commonly known as Epstein Barr[10]. The patient, by clinical criteria, presented an infection by herpes virus type three or varicella zoster, and subsequently, a hemophagocytic syndrome, since she met five of the eight diagnostic criteria according to the HLH-2004 guideline[12] (see Table 2), which gives relevance to the diagnosis. The treatment of this syndrome aims to modulate the pathological immune response it produces, with a scheme of etoposide and dexamethasone[13,14]. If triggered by infection, aggressive therapeutic management is recommended, according to the focus of infection, the suspected or confirmed etiologic agent and the clinical status of the patient.

Multiple complications of varicella have been reported, including pneumonia, bacterial infections, hemorrhagic disorders and encephalitis; age and immunological status are described as important factors for the development of complications; the age group with the highest risk of complications

Table 1. Laboratory analysis

Laboratory data	Unit	Reference data	Days of evolution											
			3	6	7	8	11	12	13	15	16	17	18	19
Hematocrit	%	33-36 %	34.7		27.0	25.2	31.0	22.3	20.6	38.0		28.0	22.9	29.2
Hemoglobin	g/dL	10.5-12.0 g/dL	11.3		10.5	9.3	11.3	8.2	7.4	14.8		8.8	10.7	10.7
Leukocytes	10^3/µL	6-17 ×10^3/µL	12.7		13.9	9.2	2.9	2.2	1.9	1.2		0.5		0.2
Neutrophils	%	20-40 %	85.0		79.6	63.0		49.0	78.8	29.5		44.5		
Lymphocytes	%	4-10.5 %	12.2		16.4	34.4		97.0						90.0
Platelets	10^3/mL	150-350 10^3/mL	346		260	146	20	14	50	25		4	10	20
Na	mEq/L	133-145 mEq/L		125	137	130	130		128		138		131	118
K	mEq/L	3-5 mEq/L		3.4	3.22	4.17	4.3		2.43				4.71	5.7
Ca	mg/dL	8-10.5 mg/dL		8.1	7.85	8.09	8.0			6.8	6.4		7.41	7.2
Glucose	mg/dL	60-100 mg/dL			122	143							154	191
UN	mg/dL	5-18 mg/dL			7.30	5.10	5.20						21.0	
Cr	mg/dL	0.2-0.4 mg/dL			0.18	0.11							0.18	0.41
PT	s	12.1-14.5 s			11.1	11.8	11.31			12.1			16.7	14.6
PTT	s	33.6-43.8 s			19	28.2	31			30.1			34.8	42.0
Fribrinogen	g/L	1. 62-4.01 g/L			117	106	204			411			416	241
AST	U/L	13-35 U/L			1 054	1 784	124						49.0	42.0
ALT	U/L	5-45 U/L			416	775	156						22.0	19.0
LDH	U/L	110-295 U/L			3 847								1 161	
Albumin	g/dL	3.6 - 5.2 g/dL			2.4	2.0	2.6			1.8	2.5			
Ferritin	ng/mL	7-140 ng/mL			1 000								1 500	
Dimer D	mg/L	0-0.5											4.26	
CRP	mg/L	0-0.9	23.7		2.13		21.0	19.4					23.8	
Urine culture				Neg		Neg								
Pharyngeal exudate culture				Neg										
IgM for SARS-CoV-2			Neg		Neg									
IgG for SARS-CoV-2			Neg		Neg									

Neg: Negative.

Source: Data obtained from clinical records.

Table 2. Criteria for the diagnosis of hemophagocytic syndrome according to the lymphohistiocytosis guideline. Hemophagocytic syndrome-2004

Diagnostic criteria	Patient criteria
Fever greater or equal than 38.5 °C	Yes
Splenomegaly	Yes
Cytopenias affecting at least two of the three peripheral blood lineages	Yes
Hemoglobin less than 9 g/L	Yes
Platelets < 100 ×109 /L	Yes
Neutrophils < 1 ×109 /L	Yes
Hypertriglyceridemia (fasting, ≥ 265 mg/dL) and/or hypofibrinogenemia (≤ 150 mg/dL)	Yes
Hemophagocytosis in bone marrow, liver, spleen or lymph nodes	Not performed
Low or absent NK cell activity	Not performed
Ferritin ≥ 500 ng/mL	Yes
SIL-2R ≥ 2400 U/mL	Not performed

Source: HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis.

is those over 15 years old, children under one year old, newborns and immunocompromised patients[15,16].

By October 18, 2021 1413 cases of chickenpox were reported in the country and two deaths due to the virus, the first, a 52-year-old female patient and the second, the patient described above, who was a female of 14 months old[17]. This is a significant difference with the region of Tucumán in Argentina, which reports 4777 cases of chickenpox per year. The vaccine has been implemented against this disease since 2015[17].

The incubation period was possibly 20 days prior to the onset of symptoms, taking the maximum incubation period of the disease. Children with chickenpox can transmit the virus through the respiratory tract one to two days before the onset of rashes, until all lesions are crusted[18]. The patient started with cutaneous lesions on the fourth day of her evolution and was able to transmit it from the second day. In immunocompromised patients, the period of transmissibility may be prolonged[18].

Hand washing with soap and water is important to prevent the occurrence of cases; when secretions are to be handled, the use of gloves is recommended, followed by hand washing[19]. If the patient is within the period of respiratory transmission of the virus, the use of an N95 mask is recommended. In the event that it cannot be used, it is recommended that the personnel in contact be the one to protect themselves with the mask and maintain a distance of at least one meter[19].

Epidemiological prevention measures are the basis for cutting the chain of transmission. They also prevent the spread of the virus. Besides, they include timely isolation, which is of utmost importance to control the disease. Moreover, it prevents the occurrence of more cases, outbreaks and deaths. Likewise, an active search for cases in the community, vaccination campaigns and timely isolation of cases should be carried out.

For the data collection, there was no availability to the clinical records of the private health center. In fact, it is considered a shortcoming affecting the integration of the continuous care.

Varicella is an endemic disease in El Salvador. Cases of this disease are more frequent in children under ten years old[3], which gives relevance to this case report. The death of the female patient after 17 days of stay in two centers a consequence of complications such as pneumonia, hemorrhagic disorders and hemophagocytic syndrome, in addition to varicella.

Ethical aspects

In accordance with the principles in the Declaration of Helsinki, this case report was developed in accordance with the Belmont Report principles of non-maleficence and confidentiality, since no patient identification data are disclosed. Informed consent was requested from the patient's parents for the presentation of this case.

Acknowledgements

Thanks to Dr. Elmer Mendoza and Dr. Claudia Zavaleta for their support in the preparation of this scientific article.

References

1. Zhang L-N, Guo W, Zhu J-H, Guo Y. Successful rescue of acute liver failure and hemophagocytic lymphohistiocytosis following varicella infection: A case report and review of literature. World J Clin Cases. 2018;6(13):659-665. DOI: 10.12998/wjcc.v6.i13.659
2. Astudillo P. P, Parejas T. C, Wietstruck P. MA, Morales M. P, Abarca V. K, *et al.* Síndrome hemofagocítico: Caracterización clínica y

seguimiento de una cohorte pediátrica chilena. Revista chilena de infectología. 2021;38(3):423-431. DOI: 10.4067/S0716-10182021000300423
3. Heymahn D. El control de las enfermedades transmisibles. 17th ed. Washintong D.C.: American Public Health Association; 2001
4. Londres HD, Izquierdo EV, Marrero LR. Neumonía por varicela. Revista Cubana de Medicina Intensiva y Emergencias. 2019;18(1):1-10. Available in: https://revmie.sld.cu/index.php/mie/article/view/577
5. Nakandakari MD, De La Rosa DN, Arias J. Varicela en un lactante. Rev Med Hered. 2018;29(3):201-202. DOI: 10.20453/rmh.v29i3.3410
6. Breuer J, Fifer H. Chickenpox. BMJ Clin Evid. 2011;4:0912. Available in: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275319/
7. Ávila-Agüero ML, Beltrán S, Castillo JB, Castillo Díaz ME, Chaparro LE, Deseda C, *et al.* Varicella epidemiology in Latin America and the Caribbean. Expert Review of Vaccines. 2017;17(2):175-183. DOI: 10.1080/14760584.2018.1418327
8. Torres Rivera LE. Varicela Zoster complicada en los pacientes menores de 12 años del Hospital Nacional de Niños Benjamín Bloom en el periodo del 01 enero de 2008 al 31 de diciembre de 2018. El Salvador: Universidad de El Salvador; 2020. Available in: https://ri.ues.edu.sv/id/eprint/24614/1/617-11106343.pdf
9. Ministerio de salud. Esquema Nacional de Vacunación, El Salvador 2021. Ministerio de Salud. Fecha de consulta: 22 de junio de 2022. Available in: https://www.salud.gob.sv/servicios/esquema-nacional-de-vacunacion-el-salvador-2021/
10. StatPearls. Treasure Island. In: Treasure Island. Vol. 1. 2nd ed. StatPearls Publishing; 2022.
11. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. Lancet Infect Dis. 2007;7(12):814-822. DOI: 10.1016/S1473-3099(07)70290-6
12. Henter J-I, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, *et al.* HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr. Blood Cancer. 2007;48(2):124-131. DOI: 10.1002/pbc.21039
13. Johnson TS, Terrell CE, Millen SH, Katz JD, Hildeman DA, Jordan MB. Etoposide selectively ablates activated T cells to control the immunoregulatory disorder hemophagocytic lymphohistiocytosis. J Immunol. 2014;192(1):84-91. DOI: 10.4049/jimmunol.1302282
14. Carranza Matamoros F, Márquez ED, Varela D, Mejía MR, Rivera MF, Soto RJ. Caracterización epidemiológica de varicela, en Región Sanitaria Metropolitana del Distrito Central, Honduras, 2016. Revista de la facultad de ciencias médicas (Impresa). 2020;17(2):17-24. Available in: http://www.bvs.hn/RFCM/pdf/2020/pdf/RFCMVol17-2-2020-4.pdf
15. Porras MH, Bejarano JIC. Varicela: «una enfermedad benigna». Rev Latin Infect Pediatr. 2017;30(3):91-92. Available in: https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDArtículo=75086&id2=
16. Cruz JGP, Hernández PR, Amaya MAT, Valencia MEM. Choque séptico por fascitis necrotizante secundario a infección por varicela; tratamiento y uso de hemoglobina en espray en terapia intensiva: presentación de caso. 2017;26(1):1-7. Available in: https://www.medigraphic.com/pdfs/alergia/al-2017/al172f.pdf
17. Ministerio de salud. Sistema de Morbi Mortalidad en la Web. 2022. Fecha de consulta: 22 de junio de 2022. Available in: https://simmow.salud.gob.sv/
18. Li R, Tian S, Zhu Y, Yan L, Zhu W, Quan H, *et al.* Management of orbital invasion in esthesioneuroblastoma: 14 years' experience. Radiat Oncol. 2019;14(1):107. DOI: 10.1186/s13014-019-1313-1
19. Dulguerov P, Allal AS, Calcaterra TC. Esthesioneuroblastoma: a meta-analysis and review. Lancet Oncol. 2001;2(11):683-690. DOI: 10.1016/S1470-2045(01)00558-7