Um Caso Clínico de Síndrome de Evans Provavelmente Desencadeada por Vacina BNT162b2 SARS-CoV-2

Evans Syndrome Probably Secondary to BNT162b2 SARS-CoV-2 Vaccine: Case Report

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Resumo:

A síndrome de Evans é rara, existindo poucos casos descritos de associação a vacina mRNA SARS-CoV-2, nenhum deles em Portugal.

Doente do sexo masculino de dezoito anos, admitido por dor abdominal, icterícia, urina escura e cansaço. Na avaliação apresentava anemia hemolítica autoimune por anticorpos quentes, tendo desenvolvido posteriormente trombocitopenia autoimune. Dos antecedentes destacava-se vasculite IgA aos vinte meses e administração de vacina mRNA SARS-CoV-2 nove dias antes da admissão. Foram excluídas infeções virais, doenças autoimunes/linfoproliferativas, imunodeficiências, fármacos e trombofilias. Apesar de não ter apresentado resposta inicial a corticoterapia e imunoglobulina, verificou-se evolução favorável após a introdução de rituximab e ciclofosfamida.

Dada a relação temporal e a exclusão de outras causas, foi efetuado o diagnóstico de síndrome de Evans provavelmente desencadeado por vacina mRNA SARS-CoV-2. É o primeiro caso descrito em Portugal e retrata uma idiossincrasia rara, não devendo desencorajar a vacinação na população.

Palavras-chave: Anemia Hemolítica Autoimune/induzida quimicamente; Vacina BNT162b2; Vacinas contra COVID-19.

Abstract:

Evans syndrome is a rare condition. There are few case reports of Evans syndrome following SARS-CoV-2 mRNA vaccine, none in Portugal.

An eighteen-year-old male patient was admitted with abdominal pain, jaundice, dark urine, and fatigue. The evaluation performed was consistent with warm autoimmune hemolytic anemia, but he later developed autoimmune thrombocytopenia. His medical history was notable for IgA vasculitis at the age of 20 months and SARS-CoV-2 mRNA vaccination nine days before admission. Viral infections, autoimmune/lymphoproliferative diseases, immunodeficiencies, medications and thrombophilia were excluded. Although he did not initially respond to corticosteroids or immunoglobulin, he responded favorably to rituximab and cyclophosphamide.

Given the temporal association and the exclusion of other causes, we can assume Evans syndrome probably secondary to SARS-CoV-2 mRNA vaccine. It is the first case in Portugal and describes a rare idiosyncrasy. It should not discourage vaccination at the population level.

Keywords: Anemia, Hemolytic, Autoimmune/chemically induced; BNT162 Vaccine; COVID-19 Vaccines.

Introduction

Evans syndrome (ES) is a rare disorder (estimated incidence of 1-9 cases/million people/year) characterized by the concurrent or sequential association of autoimmune cytopenia, usually autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), and rarely autoimmune neutropenia.[1] ES can be classified as primary or secondary, with up to 50% of ES cases being secondary to a variety of conditions, including infections, primary immunodeficiencies, systemic autoimmune diseases and lymphoproliferative syndromes.[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiologic virus of the 2019 coronavirus disease pandemic. SARS-CoV-2 vaccines (SCV2v) were one of the most important interventions to end the pandemic and prevent the emergence of new variants. The mRNA (BNT162b2; mRNA-1273) or adenoviral vector-based (ChAdOx1 nCoV-19; Ad26.CoV2.S) vaccines are the most commonly used SCV2v in Western countries.[2] Autoimmune hematologic (AIH) disorders have been reported as rare adverse events (AEs) following SCV2v exposure and can be life-threatening.[2] The reported incidence of ES secondary to BNT162b2 vaccine in Europe, Canada and the United Kingdom through March 2022 was 0.01 per million doses,[2] making ES one of the less common AIH AEs after SCV2v. To date, there is no published case report of this serious AE in Portugal.

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Case Report

An 18-year-old male was admitted with abdominal pain, jaundice, dark urine, fever (38.5°C axillary), and fatigue. He had been admitted the day before for generalized abdominal pain, dyspnea, headache and fatigue, and was discharged after being diagnosed with an anxiety episode. He denied nausea, vomiting, chest pain, gastrointestinal/genitourinary bleeding, xerostomia/xeropthalmia, arthralgia, photosensitivity, Raynaud's phenomenon, use of antibiotics or other medications.

Past medical history included IgA vasculitis at 20 months of age with inconclusive workup and undiagnosed enteropathy for which he was admitted to the pediatric ward at 4 years of age. At that time he had abdominal pain, diarrheal episodes associated with food refusal and weight percentile loss (<5th percentile for weight). The workup performed at that time is shown in Table 1. He also had a bilateral red eye episode at 16 years of age (not otherwise specified), and at 18 years oof age (7 months before his admission) he went to a gastroenterology appointment because of the previous abdominal pain and loose stool episodes that had been occurring monthly for about a year. The workup performed at this time is shown in Table 1. He had no anemia or thrombocytopenia, and total immunoglobulin E was 301 U/mL (<100). Metronidazole 500 mg 12/12 hours for 10 days for 2 consecutive months, albendazole 400 mg in a single dose repeated after 3 weeks and *Lactobacillus rhamnosus GG* were prescribed and he became asymptomatic.

He was not on regular medication and the national vaccination program had been updated. He received the first dose of BNT162b2 mRNA SARS-CoV-2 vaccine 9 days before presenting to the hospital.

On admission, he had fever (tympanic temperature 38.9°C) and jaundice. His blood pressure was 120/70 mmHg, his heart rate was 100 bpm, and he was eupneic on room air. The abdomen was unremarkable.

Table 1: Workup performed by gastroenterology years/months before being admitted.

Parameter	4-years-old	Units	Reference Value	18-years-old	Units	Reference Value
Hemoglobin	11.7	g/dL	11-14	15.6	g/dL	13-17.5
Leukocyte	6.82	x10^9/L	5-15	4.5	x10^9/L	4-11
Platelets	363	x10^9/L	200-450	260	x10^9/L	150-450
ANA	positive, 1/160			positive, 1/160		
Complement	C3 1.3 C4 0.35 CH 50 64.7	g/dL g/dL U/mL	0.9-1.8 0.1-0.4 31.6-57.6	-		
Anti-lkm	-	2.5	2.5	negative		
Anti-ds-DNA	negative	0.1	0.1	negative		
Aga	negative	0.0	0.0	-		
Ata	negative	1.4	1.4	negative		
ESR	11	0.5	0.5	11	mm/h	≤10
La	negative	161	161	-		
Aca	negative	1.5	1.5	-		
Total IgE	14.5	47	47	301	U/mL	<100
Fecal elastase	-			normal		
Fecal calp.	-			12	µg/g	<80
IgGs	IgG 13.1 IgA 1.97 IgM 1.49	g/L g/L g/L	6.4-14.2 0.52-2.2 0.4-1.8	-		
T. bilirubin	5	µmol/L	2-18	-		
Hbt	unremarkable					
Ocp	negative					
Hcb	moderate unspecific lymphoplasmacytic infiltrate					

ANA – antinuclear antibody; ASMA - anti-smooth muscle antibody; Anti-lkm - anti-liver-kidney microsome type 1 antibody; Anti-ds-DNA - anti-double stranded DNA antibody; Aga - antigliadin antibody; Ata - anti-transglutaminase antibody; ESR - erythrocyte sedimentation rate; La – lupus anticoagulant; Aca – anti-cardiolipin antibody; Total IgE – total immunoglobulin E (IgE); Fecal calp. – fecal calprotectin; IgGs – immunoglobulins; T. bilirubin – total bilirubin; Hbt – hydrogen breath test; Ocp - ova, cysts and parasites stool test; Hcb - histology from a colon biopsy

Admission blood tests revealed anemia (hemoglobin [Hb] 11.3 g/dL) and elevated lactate dehydrogenase (LDH) (1109 U/L) (Table 2). Urinalysis had blood (+++), leukocytes (+), and urine sediment had some erythrocytes. After 24 hours Hb had dropped to 7.9 g/dL, total bilirubin was high (7.5 mg/dL) at indirect bilirubin cost, and haptoglobin was decreased (8 mg/dL) Table 2. Peripheral blood smear showed no schizocytes but anisocytosis with predominant microcytosis. Direct antiglobulin test (DAT) was positive (positive IgG, positive IgG+C3d). Having warm AIHA, he was started on methylprednisolone 1 g/day for five days and folate 5 mg/day. SARS-CoV-2 test was negative. The body CT scan did not show splenomegaly and he didn't meet the criteria for hemophagocytic lymphohistiocytosis (Table 2). Sixty hours after admission, Hb dropped to 3.2 g/dL. He received 2 red blood cell transfusions (RBCT) and intravenous immunoglobulin 1 g/kg/day (50 g) for 2 days was added to methylprednisolone. At 72 hours after admission, he still had an Hb of 4.7 g/dL despite the therapeutic measures given (Table 2). One RBCT was given and he was then transferred to our hospital. Hb evolution and therapeutic interventions are shown in Fig. 1.

Table 2: Blood test from admission until the day he was transferred to our hospital.

Parameter	admission	24h ad	36h ad	48h ad	60h ad	72h ad	units | reference value
Hemoglobin	11.3	7.9	6.6	5.6	3.2	4.7	g/dL | 13.6-18
MCV	86.8	91.2	92.9	93.4	90.1	88.1	fL | 80-97
MCHC	37.1	38.6	38.9	40.1	41.7	38.2	g/dL |32-36
Leukocyte	9.4	8.6	11.7 (N 69%)	10.7 (N 86,7%)	17.6 (N 84,9)	24.5 (N 81,9%)	x10^9/L | 4-10
Platelets	212	169	188	209	241	-	x10^9/L | 140-440
PT	15.6 INR 1.4	14.6 INR 1.3	13.8 INR 1.2	13.8 INR 1.2	15.3 INR 1.3	15.3 INR 1.3	seg | 9-13
PTT	33	-	-	25	17	23	seg | 25.1-36.5
D dimer	-	-	24739	20586	-	15341	ng/mL | <500
Fibrinogen	-	-	350	406	-	265	mg/dL | 200-393
Urea	40	-	36	41	-	45	mg/dL | 18-45
Creatinine	0.79	-	0.7	0.65	-	0.7	mg/dL | 0.7-1.3
AST	73	91	119	-	147	108	U/L | 5-34
ALT	23	23	28	-	35	31	U/L | 9-24
LDH	1109	1650	2171	2544	3398	2816	U/L | 125-220
T. bilirubin	-	7.5	11.7	10.9	9.4	3.6	mg/dL | 0.2-1.2
I. bilirubin	-	6.7	9.7	9.3	8.3	2.4	mg/dL | 0-0.6
Reticulocyte	-	-	-	2.6	-	-	% | 0.5-2.5
Haptoglobin	-	8	-	-	-	-	mg/dL | 14-258
CRP	8.8	10.9	-	-	-	10.8	mg/dL | <0.5
PCT	-	1.12	-	-	-	0.99	ng/mL | <0.5
TIBC	-	<25	-	-	-	-	µg/dL | 69-240
Transferrin	-	240	-	-	-	-	mg/dL | 174-364
Ferritin	-	10 860	-	-	-	-	ng/mL | 11.1-171.9
B12 vitamin	-	185	-	-	-	-	pg/mL | 187-1059
Folate	-	2	-	<1.5	-	-	ng/mL | 5.3-14.4
Triglyceride	-	-	-	198	-	-	mg/dL | <150

24h ad – 24h after admission; 36h ad – 36h after admission; 48h ad - 48h after admission; 60h ad – 60h after admission; 72h ad - 72h after admission; MCV - mean corpuscular volume; MCHC - mean corpuscular hemoglobin concentration; N – neutrophils; ESR - erythrocyte sedimentation rate; PT - prothrombin time; PTT - partial thromboplastin time; AST - aspartate aminotransferase; ALT - alanine aminotransferase; LDH - lactate dehydrogenase; T. bilirubin – total bilirubin; I. bilirubin – indirect bilirubin; CRP - C-reactive protein; PCT – procalcitonin; TIBC - total iron binding capacity;

Figure 1: Hemoglobin and platelets evolution with therapeutic interventions. Description: A (26/8): methylprednisolone 1 g; B (27/8) 2 red blood cell transfusion + intravenous immunoglobulin 1 g/kg/day for 2 days; C (28/8) 1 red blood cell transfusion; D (30/8): rituximab 375 mg/m^2 + cyclophosphamide 750 mg/m^2 + 3 red blood cell transfusion + low molecular weight heparin 60 mg; E (31/8): prednisolone 2 mg/kg/day (50 mg 12/12h) (methylprednisolone was stopped) + non-fractionated heparin perfusion (low molecular weight heparin was stopped); F (2/9): bivalirudin perfusion was started (non-fractionated heparin perfusion was stopped); G (5/9): dabigatran 150 mg 12/12 hours was started (bivalirudin perfusion was stopped); H (6/9): rituximab 375 mg/m^2; I (13/9): rituximab 375 mg/m^2; J (20/9): rituximab 375 mg/m^2 + prednisolone was tapered to 50 + 40 mg; K (24/9): prednisolone was tapered to 50+30 mg. The shaded zone represents the period he was discharged.

On the internal medicine ward he became more tired, polypneic with oxygen 4 L/min by nasal cannula, had dark urine and Hb decreased from 4.6 to 3.6 g/dL. DAT was positive for IgG1-type autoantibody with title 4 (after steroid) and anti-e specificity. A RBCT was given and he was started on rituximab 375 mg/m^2 and a single dose of cyclophosphamide 750 mg/m^2. Urinalysis had erythrocyte/Hb +++ but sediment had no erythrocyte suggesting it was Hb. Abdominal ultrasound showed mild hepatomegaly, regular liver contour and homogeneous parenchyma, without splenomegaly. CT scan with contrast showed bilateral pulmonary embolism (PE) in the lobar arterial and peripheral branches with pulmonary infarction in the right inferior lobe.

He was transferred to intensive medical care, received 2 more RBCTs, and after the 5th day of methylprednisolone, was switched to prednisolone 2 mg/kg/day. He was also started on anticoagulation with non-fractionated heparin. Thrombocytopenia began after initiation of anticoagulant therapy (Fig. 1). Heparin-induced thrombocytopenia was negative but it needed to be confirmed with an anti-heparin-PF4 antiplatelet antibody result and it was not immediately available. So the non-fractionated heparin was stopped and he was started on bivalirudin perfusion. After 3 days in the intensive care unit, he returned to the medical ward with Hb 4.7 g/dL, platelets 70x10^9/L and under bivalirudin perfusion. Weighing the risk of bleeding and after resolution of the thrombocytopenia, bivalirudin perfusion was stopped due to the difficulty in assessing the therapeutic target and he was started on dabigatran 150 mg 12/12 hours as it had an antidote. Antiplatelet antibody by indirect method was positive for glycoprotein IIb/IIIa. Bone marrow biopsy showed normocellular bone marrow and erythroid hyperplasia without atypical elements. Paroxysmal nocturnal hemoglobinuria was excluded. Ophthalmologic examination was unremarkable. Viral infection, systemic lupus erythematosus (SLE), rheumatoid arthritis, scleroderma, celiac disease, lymphoproliferative disorders and immunodeficiency were excluded. First ANA measurement was positive (1/160), with low positive anti-SSA antibody (36.5 UQ (<20)), complement C3 slightly low 79 mg/dL (90-180), C4 and CH50 ok, negative antiphospholipid antibodies. Unexpected events were a urinary tract infection (*Escherichia coli)* and a possible pulmonary infarction infection. Piperacillin/tazobactam was given for 7 days with symptom resolution.

There were no hemorrhagic complications on dabigatran. He was maintained on weekly rituximab for 4 weeks and the evolution was favorable (Table 3, Fig. 1), so steroid tapering was started. He was discharged and followed up on an outpatient basis. Inflammatory bowel disease was ruled out. The anti-heparin PF4 antiplatelet antibody result was obtained 3 weeks after discharge and was negative. ITP was diagnosed.

Repeated ANA were negative, C3 complement was restored (120) and he had a one-time positive lupus anticoagulant while on dabigatran. Repeat lupus anticoagulant was negative. Anticoagulation was discontinued after one year because PE was considered an AIHA and an acute disease-related prolonged immobilization complication. By temporal association and after exclusion of other causes, SCV2v-induced ES was diagnosed. The steroid was tapered for 6 months with azathioprine (100 mg) until discontinued and azathioprine was also discontinued. He's currently off medication and has no anemia or thrombocytopenia.

Table 3: Blood test from the day he started rituximab to the last appointment.

Parameter	1st rituxi + cyclo	2nd rituxi	3rd rituxi	4th rituxi	dh	6mad	15mad	units	reference value
Hemoglobin	3.6	3.9	6.9	9.3	10.2	14.4	14.8	g/dL	13-17.5
MCV	89.4	109.9	114.1	106.66	105	83.4	86.3	fL	80-97
MCHC	36.1	32.7	33.6	35.3	35.3	34	33.5	g/dL	31.5-35.5
Leukocyte	45.1 (N 78.9%)	14.2	2.5 (N 65.4%)	3.8 (N 72.1%)	3.6	3.8	5.2	x10^9/L	4-11
Platelets	180	212	191	280	279	275	281	x10^9/L	150-450
ESR	-	-	-	-	-	5	11	mm/h	≤10
PT	16.4 INR 1.47	12.6 INR 1.1	-	11.2	-	-	11.4 INR 1.01	seg	11.6
PTT	23.2	23.9	-	23.9	-	41	32.5	seg	29
D dimer	-	22.02	-	1.7	-	-	0.28	ng/mL	0-0.5
Fibrinogen	151	272	-	175	-	-	-	mg/dL	200-400
Urea	54	36	32	44	24	27	31	mg/dL	16-49
Creatinine	0.74	0.43	0.43	0.44	0.36	0.77	0.83	mg/dL	0.7-1.2
AST	107	117	29	19	20	19	18	U/L	0-40
ALT	57	175	54	36	47	22	12	U/L	0-41
LDH	3422	3554	1340	485	343	169	163	U/L	100-250
T. bilirubin	3.56	2.86	1.51	0.7	0.61	0.5	0.6	mg/dL	<1.2
I. bilirubin	-	2.06	1.01	0.42	-	-	-	mg/dL	<0.6
Reticulocyte	6	9.7	-	-	-	0.9	-	%	
Haptoglobin	<10	<10	-	-	-	132	-	mg/dL	30-200
CRP	3.53	0.7	0.05	<0.03	<0.03	0.03	0.1	mg/dL	<0.5
PCT	0.82	0.77	0.1	<0.02	0.06	-	-	ng/mL	<0.5
Iron	247.8	-	-	-	-	71.9	-	ug/dL	33-193
TIBC	293	-	-	-	-	337	-	ug/dL	250-450
Ts	85	-	-	-	-	21	-	%	26-42
Ferritin	4003	-	803	-	-	371	-	ng/mL	30-400
B12 vitamin	675	-	-	-	-	295	-	pg/mL	195-770
Folate	2.6	-	-	-	-	7.8	-	ng/mL	4.6-18.7
Triglyceride	222	224	210	-	-	115	-	mg/dL	<150

1st rituxi + cyclo – before 1st administration of rituximab and cyclophosphamide; 2nd rituxi - before 2nd administration of rituximab; 3rd rituxi - before 3rd administration of rituximab; 4th rituxi - before 4th administration of rituximab; dh – the day we has discharged; 6mad – 6 month after admission (without steroids); 15mad – 15 months after admission (without any medication); MCV - mean corpuscular volume; MCHC - mean corpuscular hemoglobin concentration; N – neutrophils; ESR - erythrocyte sedimentation rate; PT - prothrombin time; PTT - partial thromboplastin time; AST - aspartate aminotransferase; ALT - alanine aminotransferase; LDH - lactate dehydrogenase; T. bilirubin – total bilirubin; I. bilirubin – indirect bilirubin; CRP - C-reactive protein; PCT – procalcitonin; TIBC - total iron binding capacity; ts - transferrin saturation;

Discussion

ES clinical features are associated with anemia and thrombocytopenia including pallor, fatigue, petechiae, ecchymosis, gingival bleeding, epistaxis[3] or jaundice, fever, shock, lumbar pain and dark urine in acute cases[2] as in our patient's case since he presented with fatigue, jaundice, fever and dark urine.

Diagnosis of ES relies primarily on DAT positivity for warm AIHA[3] and, for ITP, on the exclusion of other causes of thrombocytopenia, with or without autoantibody positivity.[4] Up to 50% of warm AIHA cases can also activate complement, resulting in DAT positivity for IgG plus complement at low titers[4] and these cases tend to be more severe compared to those positive for IgG alone.[4] Our patient had DAT positive for IgG plus complement at low titers which may also explain the severe

presentation. He had hemoglobinuria, probably because of some degree of intravascular hemolysis and low C3, probably because of this complement activation. With resolution of hemolysis, complement was restored. He had anti-platelet type IIb-IIIa antibodies, which can be documented in 35% of individuals,[3] but other causes of thrombocytopenia were excluded like heparin-induced thrombocytopenia and vaccine-induced immune thrombocytopenia with thrombosis (he did not present with thrombocytopenia and anti-heparin-PF4 antiplatelet antibodies were negative).[2]

SCV2v can induce, with extremely low incidence,[2] severe persistent AIH conditions such as ES, which can occur predominantly in patients with underlying autoimmune disease.[5] The mechanism is not understood, although the molecular mimicry between ankyrin-1, a red blood cell membrane protein, and the SARS-CoV-2 spike protein may play a role.[2] BNT162b2 is a lipid nanoparticle encapsulated mRNA-based vaccine[6] with a reported efficacy of 95%.[2] mRNA is known to be a potent activator of autoimmunity[2] and the lipid nanoparticle component further contributes to immune activation,[2] which may also contribute to the occurrence of AIH AE.[2] This can explain our patient's BNT162b2-induced ES. There have been occasional reports of this AE. New-onset ES associated with SLE was reported after the second dose of BNT162b2 mRNA COVID-19 vaccine in a 53-year-old female.[6] De Felice *et al* reported a case of ES secondary to BNT162b2 mRNA vaccine in an 85-year-old man[7] but this report does not mention whether other causes of secondary ES were excluded.

A possible limitation of the case we present is the possibility that the patient had an undiagnosed autoimmune condition that had predisposed him to ES. Although he had been followed by his pediatrician for IgA vasculitis and positive ANA (1/160), he had not been diagnosed. Also, he was thoroughly evaluated because we needed to rule out the main causes associated with secondary ES, and we could not find an autoimmune entity by itself. We could prove that he did not have a history of anemia or thrombocytopenia because his blood tests 7 months earlier were normal. Other causes associated with secondary ES were ruled out. But we cannot say that SCV2v was the only etiologic factor for ES. It is possible that he had some underlying autoimmune predisposition/condition that was triggered by the SCV2v.

This case was challenging considering due to the patient's age and life-threatening condition. The need for rituximab/cyclophosphamide and the need for therapeutic anticoagulantion with extremely low Hb levels were also challenging steps. It describes a successful management of ES, as the cytopenia resolved and has not relapsed since stopping the immunosuppression. Management of this patient is supported by evidence. The management of vaccine-induced ES does not differ significantly from the management of non-vaccine-induced ES.[2] It is mostly empirical with a low level of evidence8 because forms of adult ES are often excluded from clinical trials.[1] Steroids are recommended as first-line therapy. In some centers, intravenous immunoglobulin is recommended as a first-line treatment along with steroids,[3] while rituximab is the best second-line treatment option for adult-onset ES.[8] Cyclophosphamide could be given as a third or fourth-line option in refractory cases as it can induce remission in ES patients.[3] However, this case reflected life-threatening hemolysis. To treat life-threatening hemolysis, high doses of methylprednisolone are recommended based on expert recommendations[9] and rituximab should also be administered as early as possible to shorten the life-threatening period[9] and this was done. Given the time required for rituximab to be effective in warm AIHA (median 3-6 weeks, range 2-16 weeks),[10] cyclophosphamide was also administered. Our patient needed a total of 6 RBCT because he was severely symptomatic and that is the indication for transfusion due to the risk of exacerbations.[3] Our patient had PE, urinary tract and pulmonary infarction infection which supports what is written about ES, i.e., it can be characterized by several potentially fatal complications, particularly bleeding, infection, and thrombosis.[1]

ES can be a serious SARS-CoV-2 mRNA vaccine AE and clinicians must be aware of it in order to correctly diagnose, initiate treatment and avoid potentially fatal complications. To date, no other Portuguese case has been described. Although this is a serious adverse event report, it describes a rare idiosyncrasy and should not discourage vaccination at the population level. ■

Prémios e Apresentações prévias | Awards and past presentations

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Declaração de Contribuição

ISFS -Cuidados ao doente, pesquisa e elaboração do manuscrito, aprovação da versão final.

RCS -Cuidados ao doente, pesquisa de revisão teórica, revisão do manuscrito e aprovação final submetida.

CG – Cuidados ao doente, elaboração da revisão teórica, aprovação da versão final submetida.

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Contributorship Statement

ISFS - Patient care, research and drafting of the manuscript, approval of the final version.

RCS - Patient care, research and theoretical review, revision of the manuscript and approval of the final version submitted.

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