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Spontaneous Spleen Rupture: An Unexpected Consequence of Infectious Mononucleosis - A Case Report

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ABSTRACT

A 28-year-old man, with no remarkable previous medical history, was admitted in the emergency room for fever, odynophagia and colitis-like symptoms. A blood test showed neutrophilic hyperleukocytosis. An abdominal CT scan showed splenomegaly, and rupture of the spleen which prompted a surgical procedure. A posteriori blood serology examination showed increased immunoglobulins type IgM for cytomegalovirus (CMV) and Epstein Barr virus (EBV). There was no history of previous trauma. Spontaneous spleen rupture secondary to EBV infection-associated splenomegaly is a rare medical condition. It can be life-threatening and represents a diagnostic challenge as it may sometimes occur months after the viral infection. In addition it can occur without clinical signs of hemodynamic shock. The inversion of the leukocyte formula contributes to the diagnosis. The clinical presentation, the diagnostic, and the therapeutic strategy for spontaneous splenic rupture are discussed. The prophylactic management of splenectomized patients is also discussed.

Keywords: *Spleen, Spontaneous Spleen Rupture, Splenomegaly, Splenectomy, Infectious Mononucleosis, Colitis-Like Symptoms, Diagnosis, Overwhelming Post-Splenectomy Infection (OPSI)*

Case Report

A 28 year old Caucasian man was healthy up to 3 days before admission in emergency room (ER). He then experienced fever up to 38.5°C with flu-like syndrome and odynophagia. On the day of admission, he was suffering from excruciating abdominal pain, bloodless diarrhea with mucus, and tenesmus.

On admission, the patient reported neither specific medical history, nor known allergy. He was treated with paracetamol to alleviate fever and odynophagia.

He works as an order picker in a supermarket; occasionally consumes alcohol, tobacco (15 pack-years) and cannabis.

On clinical examination, the patient was in good general condition. Vital parameters showed: heart rate 87bpm, blood pressure 118/52mmHg, body temperature 38°C, SpO2 97% in room air, respiratory rate 14/min. The physical examination showed white sore throat without tonsil abscess, and no cervical lymphadenopathies. The abdomen was depressible and increased peristalsis was heard. The deep palpation was painful in the upper and lower left quadrants without defense or rebound. There was neither sign of Murphy, nor of McBurney, and the percussion of the renal compartments was painless. The rest of the physical examination was unremarkable.

Blood tests are reported in Table 1. Blood cultures (2 pairs) were negative after 6 days of incubation. Throat smear was negative. Stool culture was not done because the patient did not experience further episodes of diarrhea.

A contrast enhanced abdominal CT showed splenomegaly (SM) with large amounts of fluid in the abdominal cavity, especially in the peri-splenic and pelvic area. There was no retroperitoneal or pelvic adenomegalies, nor thickening of the intestinal track (Fig. 1).

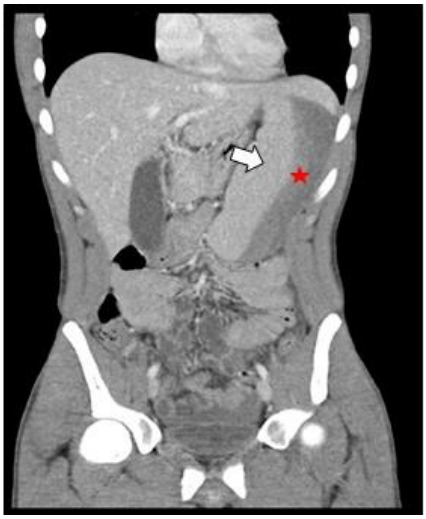

Figure 1: Abdominal CT scan after injection of contrast product – showing an enlarged spleen (white arrow) and its rupture (red star)

A laparotomy was performed without delay while the patient was still hemodynamically stable. It showed the presence of massive hemoperitoneum, extensive hepatosplenomegaly (HSM), the presence of active splenic bleeding and subcapsular hematoma, thereby leading to the indication of total splenectomy and washing of the peritoneal cavity.

The patient was hospitalized in general surgery for 7 days. The posteriori biological investigation showed IgM for cytomegalovirus (CMV) and Epstein Barr virus (EBV). The follow-up laboratory data (Table 1) showed thrombocytosis without clinical consequence.

Assessment of the seroconversion confirmed that the patient had recently been infected with EBV, rather than EBV-CMV co-infection. The infectious EBV mononucleosis was complicated with HSM and spontaneous spleen rupture (SSR).

Pathology described a spleen specimen measuring 17 x 12 x 5.5 cm and weighing 704.1 g, with the presence of a large perihilar laceration of 5 x 5 cm and extensive subcapsular hemorrhage underlying the area of laceration. The molecular analysis identified Epstein-Barr encoding region (EBER) in accordance with the serological results.

Table 1: Laboratory data

Variables	D0	D1	D2	D4	D5	D17	References
Hemoglobin (g/100ml)	13.5	13.7	11.3	12.4	13.4	13.1	13.9 – 17.7
MCV (fL)	94.7	93.4	93.8	93.1	96.1	96.1	80.0 – 95.0
WBC (/mm^3)	H 19580	H 20100	H 15820	H 13860	H 12050	9480	3790 – 10330
Neutrophil (%)	43	49	49	47	L 32.0	L 32.0	42.0 – 77.0
Absolute neutrophil (/mm^3)	H 8419	H 9849	H 7752	6514	3856	3150	1780 – 7000
Lymphocytes (%)	36	27	28	40	41	H 45.2	20.0 – 44.0
Absolute Lymphocytes (/mm^3)	H 7049	H 5427	H 4430	H 5544	H 4940	H 4280	1070 – 3120
Reactional Lymphocytes (%)	19,0	-	-	-	-	-	-
Monocytes (%)	2	H 10.0	H 11.0	6	8	H 9.4	2.0 – 9.5
Absolute monocytoscytes (/mm^3)	392	H 2010	H 1740	H 832	H 1808	H 890	24 – 730
Eosinophil (%)	L 0.0	0	0	2	3	H 10.9	0.5 – 5.5
Absolute eosinophil (mm^3)	L 0	L 0	L 0	227	362	H 1030	30 – 470
Platelets (/mm^3)	205 000	201 000	276 000	H 542 000	H 701 000	H 715 000	166000 – 389000
MPV (microns3)	8.9	8.3	8.5	8.2	9.4	7.8	5.9 – 9.9
PTT (%)	L 75	L 73	91	-	-	-	78 – 100
INR	1.13	1.14	1.05	-	-	-	0.80 – 1.20
Urea (mg/dl)	32	27	17	21	24	22	10 – 40
Creatinine (mg/dl)	0.9	0.8	0.62	0.74	0.79	0.8	0.72 – 1.25
GFR (ml/min/1.73m^2)	101	116	155	127	117	116	> 60
Total proteins (g/l)	66	L 57,0	L 52	-	-	-	64 – 83
Total bilirubin (mg/dl)	0.4	0.33	0.2	-	-	0.32	0.30 – 1.20
Direct bilirubin (mg/dl)	0.21	-	-	-	-	< 0.10	0.00 – 0.50
CRP (mg/L)	H 40.9	H 49.1	H 121.6	H 76.9	H 40.1	1.7	< 5.0
LDH (UI/L)	H 422	H 397	309	-	-	190	125 – 243
CK (UI/L)	82	H 296	1648	-	-	-	30 – 200
GOT (UI/L)	H 35	H 82	H 64	-	-	34	5 – 34
GPT (UI/L)	H 56	H 84	H 66	-	-	50	5 – 55
GGT (UI/L)	37	H 53	41	-	-	38	12 – 64
ALP (UI/L)	87	-	-	-	-	83	40 – 150

Notes : ALP : Alkaline Phosphatase ,CK: Creatinine kinase, CRP : C-reactive protein, GFR: Glomerular filtration rate, GGT : Gamma-glutamyl transferase, GOT: Glutamic-oxaloacetic transaminase, GPT: Glutamic-pyruvic transaminase, INR : International normalised ratio, LDH : Lactate deshydrogenase, MCV: Mean corpuscular volume, MPV : Mean platelet volume, Pi : Inorganic phosphorus, PTT : partial thromboplastin time, TCA, WBC: White blood cells – H : High, L : Low.

On discharge and following our local guidelines, a prophylactic antibiotic therapy with amoxicillin/clavulanate acid was prescribed, to start at the onset of a fever greater than or equal to 38°C. The patient was also prescribed vaccines (Prevenar13, Nimenrix, Bexsero, and Acthib) to be administered by his general practioner within 15 days post-splenectomy.

Discussion

Spontaneous spleen rupture (SSR) is a well-known but serious complication associated with infectious mononucleosis (IM). Its frequency varies between 0.1 to 0.5% (Sylvester *et al*., 2019; Bartlett *et al*., 2016). HSM almost always precedes SSR (Hosey *et al*., 2008). SM and its spontaneous rupture is most often associated with IM caused by EBV) (Renzulli *et al*., 2009; Ishii *et al*., 2019; Ebell *et al*., 2016), which is the leading cause of SSR of infectious origin (Renzulli *et al*., 2009).

SSR secondary to IM affects 2.5 to 4 times more males than females (2.5-4H: 1F) (Sylvester *et al*., 2019; Bartlett *et al*., 2016), and 95% of them are under 35 year-old (Bartlett *et al*., 2016).

When SM is diagnosed, it is associated with EBV infection rather than CMV infection (Ishii *et al*., 2019). In addition, when serology tests are positive for both viral capsid antigen (VCA) IgM (EBV) and CMV IgM, the latter positivity is often a false positive result resulting from antigenic cross-reactivity (Sohn *et al*., 2018). In most cases (88%), the finding of SM (with or without rupture) should prompt a search for IM (Sylvester *et al*., 2019).

To evoke the diagnosis of SSR, there should be no notion of trauma within the last 6 weeks preceding the rupture (Bartlett *et al*., 2016). The mean period of time between the onset of symptoms of IM and SSR is 14 days (Sylvester *et al*., 2019; Bartlett *et al*., 2016) with a range up to 8 weeks (Bartlett *et al*., 2016). Of note, SSR occurs within 31 days In 90 % of the cases (Sylvester *et al*., 2019), a period during which it is recommended to avoid sport activity. Bartlett *et al*, are even more drastic, increasing this recommendation up to 8 weeks (Bartlett *et al*., 2016). They also showed that only 30% of patients experience SSR within one week (< 7 days). In our case, SSR actually occurred within 3 days only, illustrating the fulminating nature of IM.

When IM is suspected, the physician should inform the patient about the risk of SSR. Information related to signs of SSR should be promptly delivered for the patient being admitted in the nearest emergency room as soon as possible. Athletes should be exempt from sport for at least 1 month (Sylvester *et al*., 2019).

Patients often complain of abdominal pain (46-88%), and left shoulder pain *i.e.* Kehr's sign (33-41%). Circulatory shock (5-27%) (Bartlett *et al*., 2016; Jehangir *et al*., 2016) can be the first feature. Asymptomatic SSR is exceptional (Jeevan and Akshay, 2008). Our patient always maintained hemodynamic stability and did not complain from left shoulder pain.

Abdominal pain in the left upper quadrant within 4 weeks of a white sore throat should suggests SM secondary to EBV IM (Sylvester *et al*., 2019; Ebell *et al*., 2016). Smith, *et al*. (1946) recommend not to palpate the abdomen as it has been reported cases of SR secondary to palpation of the spleen. They recommend of using non-traumatic methods to demonstrate SM, and SR.

Ultrasound criterion for SM is an anteroposterior spleen length > 13cm (Grover *et al*., 1993; Olson *et al*., 2015), or a spleen size greater than 11 × 7 × 5 cm (Renzulli *et al*., 2009). Abdominal doppler ultrasound appears to be ineffective in detecting acute lesions in the splenic parenchyma (Se 72-78%; Sp 91-100%) (Görg *et al*., 2003).

Abdominal computed tomography is the gold standard for detecting SM and splenic parenchymal lesions after injection of contrast product. Considering the SM diagnosis, the multiplication product of the maximum length - Lmax - (on an axial section) and the vertical height - Hvert - (on a coronal section) *i.e.* (Lmax x Hvert) greater than 115cm^2 has the strongest correlation with the actual volume of the spleen. The maximum height greater than 12cm - Hmax - (on a coronal section) also correlates with the splenic volume (Kucybała *et al*., 2018).

These parameters can be easily used by the physician in ER to diagnose SM. Fig. 2 illustrates the measurement and calculation of these different parameters in the patient.

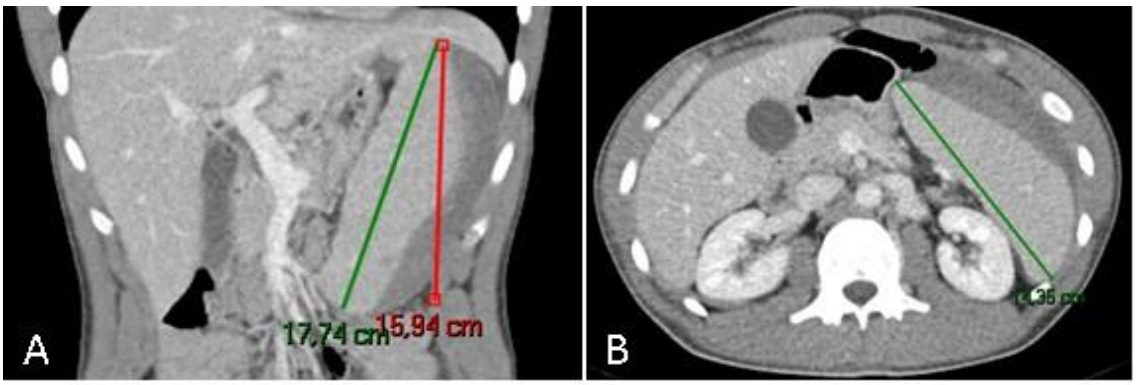

Figure 2: Enhanced abdominal CT scan showing: (A) a coronal section with Hmax = 17.74cm (green) and Hvert = 15.94cm (red) and (B) an axial section showing Lmax 14.35cm. Note: Hvert x Lmax = 228.58cm^2

IM is predominantly characterized by lymphocytic hyperleukocytosis. In the course of SSR, inversion of leukocyte formula can be observed, tipping in favor of neutrophilic predominance (Smith

EB and *S. pneumoniae* Custer, 1946). Smith, *et al*. (1946) explained this observation by the blood irritation of the peritoneum due to hemorrhage, and since the bone marrow is normal in IM, it is able to fully react to this stimulus to the point of hiding the pre-existing abnormal lymphocytosis (Smith EB and Custer, 1946). This phenomenon was observed in our patient and a re-inversion of the formula (again with lymphocyte predominance - Table 1) was observed few days after the splenectomy. Therefore, inversion of predominantly neutrophilic leukocyte formula with or without abdominal pain should prompt the clinician to rule out SSR in the setting of IM, especially in the presence of SM.

The therapeutic management of SSR is not well codified. The treatment can be surgical or not. Surgery consists mainly of total splenectomy (Renzulli *et al*., 2009; Görg *et al*., 2003), while the conservative measure consists of embolizing the splenic artery (Sylvester *et al*., 2019; Bartlett *et al*., 2016). The literature tends to favor the surgical approach by total splenectomy although the conservative option has regained interest in the recent years (Bartlett *et al*., 2016, Renzulli *et al*., 2009).

In case of massive hemorrhage or hemodynamic instability, exploratory laparotomy followed by total splenectomy remains the sole emergency treatment option (Bartlett *et al*., 2016). Our patient was always hemodynamically stable. Surgery was preferred for several reasons. First, the great SSM. Second, the spleen hematoma which was significant, and the presence of hemoperitoneum. Third, patient's excruciating abdominal pain, which was not improved after intravenous administration of opioids.

IM is a self-limiting disease that usually resolves spontaneously. The complications are airway obstruction secondary to edema, neurological damages such as meningoencephalitis and Guillain-Barré syndrome (Bartlett *et al*., 2016); SM (Sylvester *et al*., 2019; Bartlett *et al*., 2016; Ishii *et al*., 2019; Ebell *et al*., 2016; Smith and Custer, 1946) and SR (Sylvester *et al*., 2019; Bartlett *et al*., 2016; Ebell *et al*., 2016; Smith and Custer, 1946; Görg *et al*., 2003).

SM usually resolves within 3 to 4 weeks (Hosey et al., 2008). When complicated by SSR, mortality is approximately 9% (Bartlett *et al*., 2016) and occurs within 10 days following the onset of IM symptoms (Görg *et al*., 2003). Renzulli, *et al*. (2009) reported 3 factors associated with increased mortality: (1) age greater than 40 years, (2) neoplastic disorders, and (3) HSM. Noteworthy, death was neither associated with gender, nor with the choice of primary surgical or conservative treatments.

Total splenectomy is the ultimate treatment for SSR. It inevitably causes asplenia, which can be responsible for complications involving patient's vital prognosis.

Infectious complications are mediated by encapsulated bacteria, as they are often poorly opsionized and cannot longer be destroyed by the removed spleen (Rodeghiero and Ruggeri, 2012). The

most frequent infections are with those with Gram-positive diploque bacteria such as *S. pneumoniae*. Infections may also occur with Gram-negative diploque bacteria as Neisseria meningitis, and bacilli or coccobacilli, as Haemophilus influenzae type b (Buzelé *et al*., 2016; Patterson, 1996; Morse, 1996; Musher, 2020). In this context, *S. pneumoniae* is the most frequent pathogen agent responsible for the "Overwhelming Post-Splenectomy Infection (OPSI)", which is a serious and often fatal condition (Buzelé *et al*., 2016; Theilacker *et al*., 2016; Dahyot-Fizelier *et al*., 2013; Tahir *et al*., 2020). OPSI includes fulminant sepsis, meningitis or pneumonia. This occurs between 1 week up to 20 years or even 50 years after splenectomy (Buzelé *et al*., 2016; Theilacker *et al*., 2016; Tahir *et al*., 2020; Sinwar, 2014). In addition for being responsible for more than half of the purpura fulminans treated in intensive care units, *S. pneumoniae* is responsible for up to 20 % of OPSI purpura (Contou *et al*., 2020).

Prevention of this syndrome involves informing patients about the risk of infection associated with the lack of the spleen, but above all vaccination, and to a lesser extent antibiotic prophylaxis (Buzelé *et al*., 2016; Tahir *et al*., 2020). Table 2 shows the vaccination schedule the splenectomized patient must comply with. A proposal for antibiotic prophylaxis (although controversial) is shown in

Table 3 of note, in case of the patient was previously vaccinated with pneumococcal polysaccharide vaccine Pneumovax23, one must wait 3 years before starting the vaccination schedule (Buzelé *et al*., 2016). Prevenar13 provides a better response and amplifying effects compared to Pneumovax23 (Buzelé *et al*., 2016). For vaccines against N.meningitis, Nimenrix® or Menactra® are recommended (Tahir *et al*., 2020; Serra *et al*., 2018).

Annual vaccination against influenzae virus is recommended (Tahir *et al*., 2020). A recent meta-analysis (Klein *et al*., 2016) showed that *S. pneumoniae* is the main cause of surinfection in influenza-affected patients. In addition, the combination of Pneumovax23 with influenza vaccine significantly reduces the rate of pneumonia and the rate of death in elderly patients (Zhang *et al*., 2016).

Decision to use antibioprophylaxis depends on the preferences of both the patient and the physician (Davidson and Wall, 2001), taking into account epidemiological data related to antibiotic susceptibility of the main microorganisms. The latest Australian guidelines from 2019 ("Splenectomy vaccination and Antimicrobial Prophylaxis - Adult asplenic and hyposplenic patients - Clinical guideline N ° GC 257") recommend a prophylaxis of at least 3 years after splenectomy, and at least 6 months after an episode of severe infection, and lifelong antibioprophylaxis in severely immunocompromised asplenia, including individuals splenectomized for malignant hematologic diseases, and thalassemia, as well as those with sickle cell anemia (Tahir *et al*., 2020). Davidson, *et al.* (2001) recommand that to ensure proper use of antibiotics, clear and written information should be given to patients.

Table 2: post-splenectomy vaccination schedule (Buzelé *et al*., 2016; Tahir *et al*., 2020; Serra *et al*., 2018)

Bacteria	Vaccines	D0 or D14(#)	2 months(a)	5 years(a)	Every 5 years
S. pneumoniae	Prevnar13®(b)	X			
	Pneumovax®23(c)		X	X	X
N. meningitis	Nimenrix®(d)	X	X	X	X
	Menactra®(e)				
	Bexsero®(f)	X	X		
H. influenzae type b	ActHIB®	X			
Note : (#)1st dose on the day of discharge from hospital (D0) or 2 weeks (14 days) after discharge from hospital (D14) – (a)after the first dose, (b)conjugate vaccine against 13 different serotypes, (c)unconjugated vaccine from pneumococcal polysaccharide of 23 different serotypes, (d)quadrivalent conjugate vaccine with tetanus toxoid (MenACW135Y-TT)°, (e)quadrivalent diphtheria toxin conjugate vaccine (MenACW135Y-DT), (f)serogroup B vaccine (MenB) – « X » represent injections.					

Table 3: post-splenectomy antibioprophylaxis (Tahir *et al*., 2020; Davidson and Wall, 2001)

First choice	Dose	Alternatives(i)	Doses
Amoxicillin/ clavulanic acid	500/125mg 3x/day	Cefuroxime(ii)	250mg 2x/day
		Moxifloxacine(iii)	(400mg 1x/day)(iv)
		Trimethoprim/sulfamethoxazole(c)	(800/160mg 2x/day)(iv)
Notes: (i)allergic to penicillin, (ii)non IgE-mediated, (iii)Ig-E mediated, (iv)the dosages in brackets are those we suggest.			

Conclusion

We reported the case of SSR secondary to fulminant EBV IM-associated SM, occurring 3 days after the onset of IM symptoms in a 28-year-old young man with no notable risk factors. Total splenectomy is recommended but it increases the risk of OPSI, an infectious complication that must be prevented.

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