

# Sapovirus-Associated Severe, Prolonged Diarrhoea in an Autologous Stem-Cell Transplant Patient: Case Report and Literature Review

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## Abstract

This immunocompromised patient suffering from severe sapovirus colitis and enteritis became dehydrated and losing weight. He was admitted to our intensive care unit but relapsed after two months of follow-up while on intravenous immunoglobulin maintenance. Sapovirus is becoming an increasingly important pathogen responsible for sporadic and epidemic acute gastroenteritis worldwide, especially in young children. It is usually diagnosed by multiplex RT-PCR analysis of feces, which can differentiate it from other causes of infectious diarrhoea. Sapovirus does not seem to cause more severe infections in immunocompromised patients or to lead to chronic infections due to the emergence of recombinant strains, unlike norovirus, a Calicivirus with several similar features. Its potential for nosocomial epidemics is also still unclear. Most treatment of sapovirus infections focus on the symptoms as the disease is often benign. No specific antiviral treatment is presently licensed. Perhaps the proposed use of immunoglobulins or nitazoxanide to treat norovirus in immunocompromised patients could be extended to sapovirus, but these procedures remain experimental. We suggest that this increasingly important enteric pathogen that can cause severe, prolonged diarrhoea in immunocompromised patients should be closely monitored.

**Keywords:** Sapovirus; Diarrhoea; Immunocompromised patient; Intravenous immunoglobulins; Multiplex real-time RT-PCR

## Case Presentation

A man aged 44 was admitted to the hematology ward of Toulouse University Hospital in April 2017 for autologous stem cell transplantation as treatment of his Hodgkin's lymphoma.

The lymphoma was diagnosed in December 2015, with lung and colon involvement (stage IV in Ann Arbor staging system). It had relapsed after first-line chemotherapy with doxorubicin, bleomycin, vinblastine and dacarbazine, but was in complete metabolic response after a second-line treatment with bendamustine and brentuximab in June 2016. The proposed therapy was to prolong the response by performing two successive autologous stem cell transplantations. The patient was also suffering from denutrition (body mass index 18.5 kg/m<sup>2</sup>), frequent lower respiratory tract infections, pulmonary pneumocystosis in December 2016, plus an episode of *Clostridium difficile* colitis in February 2017.

The patient had been suffering from frequent liquid diarrhoea for several weeks, with no other intestinal symptoms (abdominal pain, nausea or vomiting) or fever when he was admitted. Multiplex RT-PCR for enteric viruses performed on stools revealed the presence of sapovirus. Stool analyses were otherwise negative for enteropathogenic bacteria (*Salmonella*, *Shigella*, *Campylobacter*, *E coli*) and *Clostridium difficile*. He was initially treated with 20 g/day Intravenous Immunoglobulins (IVIg). Induction chemotherapy (carmustin, cytarabine, etoposide and melphalan) was begun on April 14 and autologous stem cell transplantation was performed on April 20. The first day of chemo-induced aplasia was April 21.

His diarrhoea became worse, he became feverish, and his abdomen became distended and tender. Blood tests showed hypokalemia and hypomagnesemia requiring intravenous supplements. He also developed hypoalbuminemia and hypogammaglobulinemia that was refractory to IVIg supplements, evoking exudative enteropathy. A CT-scan showed signs of enteritis and sigmoidal colitis. The patient did not respond to broad-spectrum antibiotics (meropenem, vancomycin, amikacin, ciprofloxacin, and metronidazole) or antifungal treatment (casopfungin). He was transferred to the intensive care unit on April 26 suffering from septic shock, hypotension (mean arterial pressure 50 mmHg) and tachycardia (140 bpm). The patient was repeatedly given intravenous fluid resuscitation and antibiotics.

Subsequent stool analyses (April 19, May 16, and May 23) were still positive for sapovirus alone. Concomitant infections included an upper respiratory tract rhinovirus infection, *Staphylococcus haemolyticus* pneumonia, Epstein-Barr and BK virus-induced hemophagocytic lymphohistiocytosis that were treated with dexamethasone and IVIg.

Analysis of sigmoidal biopsies obtained by a short colonoscopy performed on May 12 showed structural distortions of the colonic mucosa (atrophic glands, hollow chorion), but no active inflammatory lesions or viral cytopathic effect. Immunohistochemical studies on the colon biopsy with anti-CMV antibody, CMV PCR and sapovirus PCR were all negative.

His condition slowly improved; the fever and diarrhoea abated after a second course of intravenous immunoglobulins on May 12th and progressive enteral renutrition *via* a naso-gastric drip. Antibiotics were gradually stopped after treatment for 21 days. The patient was then returned to the hematology ward and discharged on May 29<sup>th</sup> after resolution of his chemo-induced aplasia. The patient still had some symptoms at discharge, including episodic diarrhoea and abdominal discomfort. We proposed monthly anti-infectious intravenous prophylactic perfusions of immunoglobulins.

Diarrhoea reappeared two months later in early July 2017, with dehydration and hydro-electrolytic disturbances, needing admission to a medical ward. Stool analysis performed on August 1<sup>st</sup>, 112 days after the first stool analysis, remained positive for sapovirus. As before, there were no other enteropathogens. The patient's evolution was unfortunately unfavorable. He deceased on September 28th after a progressive deterioration of the general state, in cachectic condition with cytopenias and multiple bacterial infections (blood, urinary and lower respiratory tract).

## The Etiological Agent

### Virology

Sapovirus is responsible for acute gastroenteritis in humans and animals. It belongs to the Calciviridae family (together with norovirus, lagovirus, nebovirus, and vesivirus). The Sapovirus genus, Sapporo virus species are described in the report of the International Committee on the Taxonomy of Viruses 2016 [1]. Sapovirus particles were first observed by electron microscopy of human stool samples in 1976. These small (30-38 nm diameter) icosahedral particles have cup-shaped depressions on their surface, something like a star of David. The virus is unenveloped, making it resistant in the environment. The prototype strain, Hu/SaV/Sapporo/1982/JPN, was isolated from the Sapporo gastroenteritis outbreak in an orphanage in 1982: hence its name. While there are animal sapoviruses, zoonotic infection is not possible because there is an interspecies barrier [2-4]. Although a porcine sapovirus cell culture has been developed in a murine model, no human sapovirus cell culture model is yet available, limiting our knowledge of its replication cycle [5].

The virus genome is composed of one 7.1-7.7 kb long positive-sense, single RNA strand. The first complete genome sequence was determined for the Manchester strain Hu/Manchester/93/UK in 1993 and the full-length genome determined later was found to be 91.7% homologous to that of the Manchester strain [6]. It contains 3 distinct Open Reading Frames (ORF). ORF1 encodes a long polyprotein that is processed by the virus protease to give 6 nonstructural proteins and the major capsid protein VP1 [7,8]. ORF2 is predicted to encode the minor structural protein VP2, while the function of ORF3 in human strains remains unknown. Key enzymes involved in virus replication are the RNA-dependent RNA polymerase (RdRp) [9] and the RNA helicase eIF4A [10]. The major capsid protein VP1 is essential for the assembly of virus particles [11,12]. The VP1-encoding region is the most diverse one, as it includes a Center Variable Region (CVR). Sapoviruses are divided into genogroups and genotypes according to their VP1 genetic sequences [13]. Four human sapovirus genogroups (GI, GII, GIV, GV) have been defined, whereas genogroup III infects

pigs. Antigenicity differs among genogroups and genotypes, suggesting that the VP1 sequence is linked to virus antigenicity [14-16]. The other regions (the RdRp-region and the RdRp-VP1 junction region) are less diverse than VP1, thus less relevant for establishing a reliable classification. However they may be useful for epidemiological surveys and the characterization of recombinant strains.

Recombinant strains are defined as sapoviruses with inconsistent grouping between VP1 and the RdRp region. Recombination may occur between genogroups, or genotypes belonging to the same genogroup. The sequences of both VP1 and RNA polymerase are needed to identify recombinant viruses [17,18].

The sapovirus geno groups and genotypes in a given geographical area evolve over time [19-22]. This time-evolution pattern is probably due to the genetic diversity induced by mutations triggered by RNA polymerase activity and their selection [21]. The coexistence of several predominant strains during epidemics favors the emergence and stabilization of recombinant strains in a single geographical area [23]. Human-human transmission occurs *via* the fecal-oral pathway (either directly *via* contact with infected feces, vomitus, or indirectly *via* surfaces), or by consumption of contaminated food (especially shellfish) or water [24-26]. Sapovirus can be a public health problem as it causes outbreaks notably in health care settings, and sporadic cases worldwide. They are facilitated by a low infectious dose (1500 to 2800 genomic copies), the shedding of large amounts of virus, great environmental stability and relative resistance to disinfectants. Sapovirus is one of the most frequent agents causing acute gastroenteritis [27-31]. Outbreaks occur in people of all ages and throughout the year, unlike sporadic cases, which mostly affect children less than 5 years old, with a seasonal peak in winter [32]. Outbreaks are especially likely to occur in semi-closed settings: childcare centers, schools, hospitals, long-term care facilities, restaurants, hotels, etc. [33-36]. Sapovirus was detected in 1.3 to 22.6% of stool samples taken during gastroenteritis outbreaks [4,22, 32,37,38]. To date, the largest food-borne sapovirus outbreak occurred in Japan in 2010; it was spread by lunch boxes handled by people working in a single catering company [39]. Coinfections with other enteric viruses (adenovirus, norovirus, etc.) or other sapovirus genogroups/genotypes have been reported [24,40,41].

No host susceptibility factor to sapovirus has yet been identified. Susceptibility to human sapovirus is not associated with histo-blood antigen phenotypes, unlike sensitivity to norovirus [42]. Malnourishment and poor sanitary conditions may also be susceptibility factors [43]. The replication sites within the host, the pathological changes induced by sapovirus, and the mechanisms underlying immunity to it are yet to be characterized. Humoral protection may be involved as mother-to-child protection was reported during an outbreak in a mother/infant unit [44]. Seroprevalence reaches 90% in children and adults, suggesting that childhood sapovirus infections are common [45]. Studies using a porcine sapovirus cell culture model indicated the involvement of innate immunity factors, particularly type I interferon [46]. Protection seems to be genogroup and genotype-specific, as reinfections with different genogroup/genotype sapoviruses can occur [19,32].

### Clinical presentation

Sapovirus is responsible for acute gastroenteritis (liquid diarrhoea, vomiting, abdominal pain), with usually no fever, unlike bacterial diarrhoea. The mean incubation period is 1.7 days (less than 1 to 4 days) [47]. Other cardinal symptoms include fatigue, chills, myalgia, and headache. Rare complications include intussusception [48], and severe abdominal distension that can be mistaken for occlusive

syndrome [49]. Some people can be asymptomatic while still shedding great virus loads in their stools [4,39,50]. The disease is rapidly self-limited and is resolved within 1 week in immunocompetent patients [33,34,39,51]. Despite improvements in the intestinal symptoms, virus continues to be shed for 1 to 4 weeks after disease onset [52,53]. The gastroenteritis caused by sapovirus is reported to be less severe than that caused by norovirus or rotavirus [51,53]. Nevertheless, it can lead to hospitalization and death, especially in frail, elderly patients during outbreaks in long-term care facilities [34]. It is not yet clear whether sapovirus can cause more severe disease in at-risk patients, as does norovirus in immunocompromised persons and neonates [54,55]. There have been few reports of cases of sapovirus-induced chronic diarrhoea in immunocompromised patients [40,54]. A study on a cohort of 16 renal transplant patients suffering from chronic diarrhoea associated with calicivirus, included 1 patient who was sapovirus-positive; his diarrhoea lasted 147 days and virus continued to be shed into his gut until day 157 [54].

### Laboratory diagnosis

Several methods are used to detect sapovirus in human, usually stool, samples [56]. Diagnosis can be direct, by electron microscopy, detecting antigens or nucleic acids. Transmission Electron Microscopy (TEM) is no longer routinely performed in most laboratories. Antigens are generally detected by Enzyme-Linked Immunosorbent Assays (ELISA) [57]. Although they are very specific, these assays are less sensitive than nucleic acid detection, and they cannot detect antigenically diverse sapoviruses. A future challenge will be to develop a pangenogroup/pangenotypic ELISA or immunochromatography test, that uses a panel of broadly reactive monoclonal antibodies, or that targets a VP1 epitope common to all genogroups [58-60]. Serology enables indirect diagnosis, but is not clinically relevant as the seroprevalence in human populations is over 90% [45].

Nucleic acid detection methods are used for the routine detection of enteric viruses in clinical specimens. The most frequently used, real-time RT-PCR, is more sensitive than TEM and ELISA, and is widely available. Other methods include conventional RT-PCR with migration of amplicons by agarose gel electrophoresis and microsphere-based detection of fluorescent PCR products (Luminex technology) [61-65]. Primers may target the VP1 region, the RdRp region or the RdRp-VP1 junction region, depending on the test. Most assays include multiple or degenerate primers to cover the great genetic diversity of sapoviruses, but some may still miss particular genogroups [66]. Assays targeting the RdRp-VP1 junction region are the most sensitive and can be used as the first choice for screening clinical specimens for sapovirus. The VP1 region enables virus genotyping. RdRp primers may detect conserved patterns found in other human enteric viruses [56]. Multiplex assays for enteric viruses are the most frequently used in clinical practice. Some tests provide fast detection of viral, bacterial and parasitic enteropathogens at the same time [67-70]. Metagenomics applied directly to stool samples may become a very useful diagnostic tool in the future [71]. Full genome sequencing is not used in routine clinical practice [72].

The test used in this case was a commercial multiplex real-time RT-PCR (ALLPLEX™ GI-Virus Assay, Seegene®), that can be used for feces, rectal swabs, and intestinal biopsies. It detects 6 viral targets (norovirus GI, norovirus GII, rotavirus, adenovirus 40 and 41, astrovirus and sapovirus). For sapovirus, genogroups GI, GII and GIV are detected.

### Parallel with Norovirus

Sapovirus has several virological, epidemiological and clinical features in common with norovirus, as they both belong to the

Caliciviridae family. Like sapovirus, norovirus is a non-enveloped virus with a single-stranded, positive-sense, 7700 nucleotide-long RNA genome. It was discovered in 1972 by electron microscopic examination of feces from a subject who was part of a gastroenteritis outbreak in a school in Norwalk. The genus is made up of 6 genogroups and more than 30 genotypes, with genotype GII.4 being the most prevalent worldwide. Variant strains have been generated by mutations and recombinant strains that contribute to the great genetic diversity of norovirus [73]. There are noroviruses that infect cattle, pigs, and sheep, but transmission is species-specific and thus no zoonotic transmission has been described. While there is no culture model for human norovirus, a murine norovirus culture model has been used to study the virus life cycle and its interactions with the host immune system and microbiota [74].

Norovirus is the main agent responsible for acute gastroenteritis in adults and adolescents in the United States, and the second, after rotavirus, in young children less than 5 years old [75]. Among Nicaraguan children universally vaccinated against rotavirus, norovirus and sapovirus have become the leading causes of gastroenteritis [76]. Similarly to sapovirus, norovirus also causes sporadic and epidemic gastroenteritis. It is transmitted *via* the fecal-oral route. Its contagiousness is enhanced by the same factors as for sapovirus: low infectious doses (as low as 10 units PCR [77]; resistance in the environment, resistance to heat, low and high pH, and to usual concentrations of sodium hypochlorite-based cleaning solutions. A prolonged fecal excretion often observed after recovering also participates to the contagiousness. The globalization of the food industry may favor large norovirus outbreaks [73]. Nosocomial outbreaks are feared, especially in long-term care facilities for elderly people and immunocompromised hosts (transplant units, chemotherapy units), because of the great genetic diversity of the strains involved and the high attack (50%) and transmission rates (27%).

The morbidity and mortality rates due to norovirus are enormous, as is its socio-economic burden, quite unlike those of the much less prevalent sapovirus. It is estimated to cause around 20 million cases, 70,000 hospitalizations, and 800 deaths per year in the USA and its cost to society is estimated at around 60 billion dollars per year [78,79]. Norovirus is responsible for the death of more than 2, 00,000 children per year in developing countries [80]. Global mortality is around 0.8-2.8%, resulting from dehydration, malnutrition, sepsis, inhalation pneumopathy, but rarely from necrotizing enterocolitis, colon perforation, or acute gastro-intestinal bleeding (Mallory-Weiss syndrome) [75,81]. Genetic factors make hosts susceptible to norovirus infections. The Histo-Blood Group Antigens (HBGA) includes the ABO group and Lewis group antigens, and harbour a genetic polymorphism. Their genes encode glycan molecules (heparan sulfate, sialic acids,  $\beta$ -galactosyl ceramide) that are used by the virus to bind to and enter small intestine enterocytes, with each norovirus strain having a characteristic HBGA-binding profile. The HBGA are thus a target for developing an antiviral treatment [82].

The clinical picture is similar to that for sapovirus. Disease occurs after a short, 24-48 hour, incubation period [47]. It is mild and self-limited in immunocompetent hosts, and symptoms resolve in around 3 days. However, norovirus may cause chronic infections in immunocompromised hosts [83,84] (people with congenital immune deficiencies [85], HIV-infected hosts [86,87], cancer patients [88], people with hemopathies [88], solid organ transplant recipients [89-91], allogeneic stem cell transplant patients [88,92,93] and elderly people with comorbidities). The prevalence of norovirus infections in

immunocompromised hosts is not well-established: it may be around 17-18% [84]. It represents a challenge in terms of diagnosis (differential diagnosis notably includes graft-versus-host-disease), prevention of transmission (with a risk of nosocomial transmission and outbreaks in hospitals), and therapeutic management. Chronic norovirus infections may last for years in immunocompromised hosts, causing weight loss, graft dysfunction and decreased quality of life; it may also exacerbate the outcome of the underlying disease [54,94]. Asymptomatic healthy hosts may shed virus for weeks or months, and immunocompromised ones for years, raising the possibility of a long-lasting reservoir for future outbreaks and/or the emergence of variant or recombinant strains in individuals [90,95-97]. However, some clinical observations do not favor the emergence of new norovirus strains in chronically infected hosts [98,99]. Treatment is developed later; reducing immunosuppression, is, whenever possible, the therapeutic priority in any chronic norovirus infection, as the B-cell and T-cell responses must recover in order to clear the virus [54,100,101].

### Treatment and prevention

No specific antiviral curative treatment for sapovirus is yet available. The key features of treatment are supportive care with rehydration (oral or/and intravenous) and renutrition (sometimes enterally or/and parenterally in cases of prolonged, severe diarrhoea [100]. The experimental treatments that have been proposed for norovirus gastroenteritis, or prophylactic use in epidemics could also be applied to sapovirus infections, but none has been specifically studied. None of these strategies has been approved in clinical trials, but any that are proved to be efficient and safe could be useful in high-risk patients, including immunocompromised ones. These include: Passive immunotherapy with intravenous polyvalent immunoglobulins [102]. They act as immunomodulators, cause opsonization, and may contain specific anti-sapovirus antibodies.

- Passive immunotherapy with specific monoclonal anti-capsid antibodies can neutralize norovirus and prevent infection [60,101].

- Oral immunoglobulins seem to have reduced norovirus-induced diarrhoea in one retrospective study on immunocompromised patients, but the difference was not statistically significant. No benefit was found in terms of time in hospital or cost [103].

- Drugs targeting key factors of the virus cycle. Research has identified compounds that inhibit norovirus replication *in vitro*, some of which are also effective *in vivo* in murine models. RdRp polymerase inhibitors [9], protease inhibitors, and putative NTPase/helicase inhibitors [10] can all target specific virus proteins. The antiviral properties of interferon can be used against norovirus [46]. Novel strategies include targeting essential host cell factors, or exploiting the high mutation rate of noroviruses (ribavirin and favipiravir seem to possess lethal mutagenesis properties) [104-106]. The great genetic variability of these viruses, due to the imprecision of the viral polymerase during replication and the potential for strains to recombine, is a barrier to the development of potent drugs against norovirus and sapovirus. An efficient therapy should anticipate the risks of virus evasion by acting against all genotypes and having a high barrier to resistance. The ideal antiviral treatment should therefore combine at least two drugs whose resistance profiles do not overlap, to decrease the risk of resistant variants emerging in chronically infected patients and in outbreaks [107].

- The anti-parasitic, antiviral thiazolidine drug nitazoxanide produced a modest decrease in symptom duration in healthy

individuals, and resolved the symptoms in one patient chronically infected by norovirus [108].

- A recent drug screening seemed to indicate that theaflavins have an antiviral effect against Caliciviridae [109].

Global measures for preventing virus transmission between individuals rely on scrupulous hygiene: frequent hand-washing or the use of hand sanitizers; isolation of sick patients, especially in long-term care facilities (sick employees should respect hygiene advice even long after resolution of symptoms, as virus may be shed for several weeks); decontamination of surfaces with 0.5% sodium hypochlorite-based cleaning solutions. Most environmental prevention relies on monitoring wastewater stations and prohibiting wild rejections. RT-PCR monitoring of food production and water areas (notably shellfish farms), has been proposed to accelerate public health alerts, but the threshold for clinical symptoms and alerts, and the pertinence and cost/benefit ratio of this strategy, remain to be evaluated [110-113].

There is currently no vaccine against sapovirus. Most research is focused on finding a curative and/or preventive vaccine effective against norovirus. Creating a vaccine must overcome problems of virus diversity and incompletely understood characteristics such as virus-host cell binding and duration of immunity after infection. Identifying important capsid VP1 antigenic sites, developing improved model systems and further studies in humans will all help to design future vaccines [58]. Multivalent vaccines based on virus particles may have cross-protective activity, and seem promising in terms of immunogenicity; they could be available within 10 years. Target populations are those at risk of severe disease (immunocompromised patients and the elderly) and those at risk of propagating disease (e.g., healthcare workers); further studies will help determine the best ways to protect and prevent transmission among these groups [114,115].

### Discussion

To our knowledge, this is the first case report of life-threatening acute gastroenteritis associated with sapovirus in an immunocompromised patient. His immunodeficiency resulted from treating his Hodgkin's lymphoma with induction chemotherapy and autologous stem cell transplantation. The clinical picture was particularly severe as it occurred in a patient with other problems, including *Clostridium difficile* membranous colitis and undernourishment. His dehydration was severe enough to require massive intravenous fluid resuscitation and hydro-electrolytic supplementation, and his denutrition needed parenteral and enteral feeding; all of which led to his admission to an intensive care unit. The symptoms were not specific for an enteric virus, and undoubtedly several other factors contributed to his intestinal disease: the microbiota dysbiosis induced by using broad-spectrum antibiotics and the recent *Clostridium difficile* infection, the toxicity of chemotherapy on the gut mucosa, and a possible contribution from neutropenic enterocolitis. There was no evidence that other enteric pathogens were involved.

The diarrhoea and virus shedding continued for longer (at least 112 days) than they would have in immunocompetent patients, which is consistent with published reports. Unfortunately, quantitative PCR is not available in our laboratory; it would have been useful to compare its results to immunocompetent patients suffering from sapovirus gastroenteritis, and to monitor the intensity of virus shedding over time. We are also unable to sequence sapovirus in our laboratory, and therefore do not know its genogroup and genotype, neither could we study any recombinant strains that might have emerged during follow-up.

The diarrhoea that occurs in immunocompromised patients suffering from norovirus infection is known to be more severe and prolonged than that occurring in immunocompetent patients, but the difference with sapovirus is not clear. This case suggests that, while sapovirus is reputed to cause benign disease in young children and immunocompetent patients, it may cause severe gastroenteritis in immunocompromised subjects and therefore should not be taken lightly. As polyvalent intravenous immunoglobulins have been proposed to help cure norovirus infection, we used them in an attempt to clear this sapovirus infection [102]. The optimal dose of IVIg is not formalized. Patte, et al. [102] used 1 g/kg IVIg three times a week, then once a week depending on the symptoms. The smaller dose we used could have slowed the clinical state. Our patient was maintained on intravenous immunoglobulins for a month as an anti-infectious prophylactic measure, as is common for stem cell transplant patients. The efficacy of this strategy for preventing secondary calicivirus infections remains to be determined.

## Conclusion

In conclusion, sapovirus is a note-worthy emerging enteric virus that is similar to norovirus and may cause severe, prolonged diarrhoea in immunocompromised patients. Its potential for causing nosocomial epidemics remains to be clarified. It is diagnosed by RT-PCR analysis of fecal samples and its treatment is mainly symptomatic: intravenous or oral polyvalent immunoglobulins may be used as an experimental treatment to accelerate virus clearance, though the details of their efficacy remain to be studied.

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