

The world's first case of liver cirrhosis in a child with Castleman's disease

Castleman's disease, specifically a subtype called TAFRO syndrome, is a very rare condition that affects the patient's immune system and can, in some cases, present with severe symptoms such as internal organ failure, including liver failure. The disease has been recently identified in Japan but is relatively unknown to the rest of the world. Dr Soya Kobayashi at Okinawa Prefectural Chubu Hospital and Dr Ayano Inui at Saiseikai Yokohama City Tobu Hospital have come across the first case of a child with liver cirrhosis caused by Castleman's disease and decided to share the experience and knowledge with researchers and doctors around the world.

Lymphoproliferative disorders (LPDs) are diseases characterised by the excessive production of lymphocytes, a type of white blood cell that is part of the immune system. They are not necessarily cancerous in nature; however, the most common LPDs include a series of blood cancers (leukaemia, multiple myeloma) and lymphomas (cancer of the immune cells). In contrast, Castleman's disease is a rare and benign lymphoproliferative disorder with an estimated annual incidence of 0.24 per million in the United States and approximately 1 per million in Japan.

CASTLEMAN'S DISEASE

Castleman's disease (CD) describes a group of rare and inadequately comprehended lymphoproliferative disorders that can present with a variety of symptoms that all have in common the enlargement of the patient's lymph nodes. CD has three variants: the unicentric CD (one or more enlarged lymph nodes

present in a single area of the body), the multicentric CD of viral cause, and the idiopathic multicentric CD (iMCD). In multicentric disease, enlarged lymph nodes are present in multiple areas of the body, while idiopathic means that scientists haven't identified the actual cause and mechanisms of the disease yet. Although it has been associated with specific viral infections, such as the Human Immunodeficiency Virus (HIV) and Human Herpesvirus (HHV-8), approximately half the cases are idiopathic.

In the iMCD, also known as giant lymph node hyperplasia, symptoms, caused by the body's catastrophic inflammatory response, can range from a mild swelling of the lymph nodes to an enlarged liver (hepatomegaly), disturbance of the small vessels that lead to general swelling of the body (anasarca oedema), internal organ failure, and even death. In Japan, it is more common than the other variants of the multicentric disease and has more severe symptoms. To diagnose the disease, it is often required to exclude other diseases first, such as cancers and infectious diseases, while the doctors also need to have a high suspicion of the condition that must be confirmed by the patient's laboratory results. The nonspecific signs of the disease, in combination with its rarity and unknown causality, make it an immense diagnostic and therapeutic challenge for doctors.

TAFRO SYNDROME

iMCD can be further divided clinically into patients with TAFRO syndrome and those without TAFRO syndrome. TAFRO syndrome is a variant of the disease that has recently been reported in Japan, with the vast majority of the



Radiographic tests revealed that the patient had Castleman's disease, although the young child showed no typical symptoms of TAFRO syndrome.

disease cases so far reported there as well. Its name is an abbreviation of the signs and symptoms with which it usually presents: thrombocytopenia (low counts of platelets, the cells responsible for the blood's coagulation), anasarca oedema (generalised body swelling secondary to fluid retention), reticulin fibrosis of the bone marrow (a laboratory finding in which structural fibres are detected in the affected bone marrow by using a stain called reticulin), renal (kidney) dysfunction and organomegaly (the enlargement of one or more of the inner organs).

The TAFRO syndrome, besides being more uncommon than the rest of the CD subtypes, usually has a more critical presentation as well. TAFRO most commonly presents in middle-aged and elderly patients, and besides an isolated case described in an adolescent in 2014, there has not been a previous report of the disease in children.

AN UNLIKELY SCENARIO

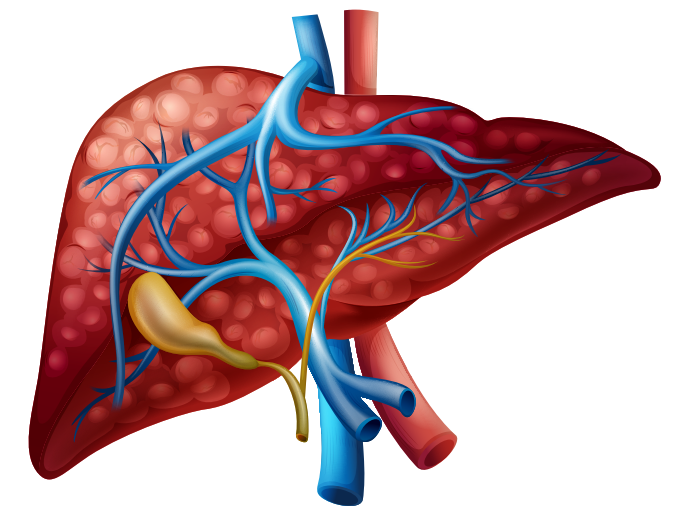
Liver cirrhosis, the end-stage liver disease caused by the formation of scar tissue, is a very rare sign of CD and has so far only been described in a couple of patients in the literature, none of them being children. In Japan, Dr Soya Kobayashi at Okinawa Prefectural Chubu Hospital

and Dr Ayano Inui at Saiseikai Yokohama City Tobu Hospital recently came across the first case of a child with liver cirrhosis caused by CD – specifically, its TAFRO syndrome variant. The challenges they faced during their effort to diagnose and

find an appropriate treatment for the patient lead the researchers to share the experience with scientists and doctors around the world, in hopes to increase the awareness of the condition.

The patient, a ten-year-old Japanese boy, attended the hospital complaining of a five-day fever. When he was examined by his doctors, he had a normal height and weight, no temperature, and he was found to have an enlarged liver (hepatomegaly), enlarged spleen (splenomegaly), and swollen lymph nodes on his neck. The doctors ran blood tests that revealed an increase in his white blood cells, low levels of red blood cells (anaemia), elevated levels of liver enzymes, and raised blood markers of inflammation. They also performed radiographic tests (abdominal computer tomography and magnetic resonance imaging) to investigate the hepatosplenomegaly. These revealed that he also had liver cirrhosis. The imaging was followed by laparoscopic (keyhole) surgery and a liver biopsy (acquisition of a tissue sample for examination under the microscope) that confirmed the liver damage diagnosis. Lymph nodes sampled from the area around the liver revealed characteristics typically seen in the TAFRO syndrome.

The nonspecific signs of the disease, in combination with its rarity and unknown causality, make it an immense challenge for doctors.



Cirrhosis is the scarring (fibrosis) of the liver as a result of long-term liver damage.



