Health & Medicine | Soya Kobayashi & Ayano Inui

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.

ymphoproliferative 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

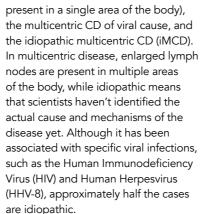
Castleman's disease (CD) describes a group of rare and inadequately comprehended lymphoproliferative disorders that can present with a variety of symptoms that all have in common the enlargement of the patient's lymph nodes. CD has three variants: the unicentric CD (one or more enlarged lymph nodes

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

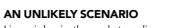
In the iMCD, also known as giant lymph node hyperplasia, symptoms, caused by the body's catastrophic inflammatory of the lymph nodes to an enlarged liver vessels that lead to general swelling of the body (anasarca oedema), internal is more common than the other variants severe symptoms. To diagnose the 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

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



response, can range from a mild swelling (hepatomegaly), disturbance of the small organ failure, and even death. In Japan, it of the multicentric disease and has more causality, make it an immense diagnostic and therapeutic challenge for doctors.



the disease in children.

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

which structural fibres are detected in the

called reticulin), renal (kidney) dysfunction

and organomegaly (the enlargement of

The TAFRO syndrome, besides being

more uncommon than the rest of the CD subtypes, usually has a more critical

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

presentation as well. TAFRO most

one or more of the inner organs).

fluid retention), reticulin fibrosis of the

bone marrow (a laboratory finding in

affected bone marrow by using a stain

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

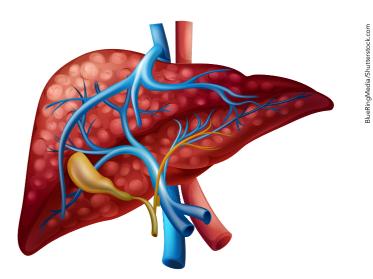
find an appropriate treatment for the patient lead the researchers to share the experience with scientists and doctors around the world, in hopes to increase the awareness of the condition.

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.



showed no typical symptoms of 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.

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The above findings led the medical team to conclude that their patient had Castleman's disease; however, the patient did not meet the diagnostic criteria for TAFRO syndrome and therefore made the diagnostic procedure challenging for the team, especially since the young patient didn't demonstrate the most typical findings of TAFRO (thrombocytopenia, reticulin

fibrosis of the bone marrow and renal failure), but rather the uncommon finding of liver cirrhosis.

The patient was initially given a trial of steroids (1 mg/kg of prednisolone daily) which is the usual regimen prescribed for CD. However, his condition did not improve, and the patient was next given tocilizumab. The treatment with

iMCD and TAFRO syndrome are conditions that should be suspected in patients with fever of unknown origin, an enlarged liver, or swollen lymph nodes.



tocilizumab (a monoclonal antibody against the interleukin-6 receptor (IL-6R), a molecule that plays an important role in immune response) eventually helped to control the fever.

IT COULD BE CASTLEMAN'S

TAFRO syndrome is a rare form of CD with an even scarcer presence in children. The challenges that come with trying to diagnose the disease have to do with the often nonspecific signs of the condition, its rarity, and also its unknown causality. Kobayashi and Inui believe that there is still a lot of research required for further understanding the disease, including its causes and its working mechanisms. This additional knowledge will help doctors develop more accurate diagnostic criteria and successful treatment strategies. This is immensely important, especially since patients with this severe form of CD present a high mortality rate and often require critical care. Thus, a definitive and early diagnosis is critical to ensure a better outcome.

iMCD and TAFRO syndrome are conditions that should be suspected in patients with fever of unknown origin, an enlarged liver, or swollen lymph nodes. Besides conducting further scientific studies, increasing awareness of the disease among clinicians could also prove very useful in early suspicion, identification and treatment of the condition that can as a result save a lot of lives.

Behind the Research



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Research Objectives

Dr Kobayashi and Dr Inui present the world's first pediatric case of Castleman's disease (CD) with liver cirrhosis.

Detail

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Bio

Soya Kobayashi, MD, specialises in pediatric hepatology, gastroenterology, and gastrointestinal endoscopy. After belonging to the Department of Pediatric Hepatology and Gastroenterology, Saiseikai Yokohama City Tobu Hospital, he currently works at the Department of Pediatrics, Okinawa Prefectural Chubu Hospital.

Ayano Inui, MD, PhD, is director of the Department of Pediatric Hepatology and Gastroenterology, Saiseikai Yokohama City Tobu Hospital.

Collaborators

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References

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Personal Response

What do you think the next steps should be to establish diagnostic criteria and treatment guidelines for children with CD?

It is important to widely recognise that CD can lead to cirrhosis, and the pros and cons of liver transplantation in cases of cirrhosis are issues for future study.



