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Caso Interactivo: Cuadro de Superposición de Dengue y Hepatitis A

Análisis de Casos

.

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RESUMEN

A continuación se presenta el caso clínico de una paciente que busca atención médica en un hospital de tercer nivel localizado en Quito, Ecuador. La paciente debuta con un cuadro febril, síntoma y signo poco específico pero con el antecedente de un viaje a un lugar tropical. El interés médico-científico es ampliar las posibilidades diagnosticas de un cuadro febril agudo. Es importante que el estudiante de Medicina y médicos estén familiarizados además con los cuadros infecciosos virales más comunes en el país. Este caso también nos da pautas para el diagnóstico de una infección viral y la consideración de infecciones concurrentes. Las infecciones virales mixtas han sido reportadas pero se plantea un mayor nivel de conciencia médica para estar alerta especialmente en regiones endémicas, en donde se pueden plantear dilemas diagnósticos, complicaciones, gasto innecesario de recursos y prolongación de curso de la enfermedad.

Palabras clave: *endémicas, tropical, viral, cuadro febril, infecciones*.

ABSTRACT

The following clinical case presented here corresponds with a patient seeking medical attention at a tertiary hospital located in Quito, Ecuador. The patient debuts with a febrile feature, which is a symptom and sign, not very specific, but with the antecedent of a trip to a tropical place. The medical-scientific interest is to expand the diagnostic possibilities of an acute febrile illness. It is important that the medical student and doctors are also familiar with the most common viral infectious diseases in the country. This case also gives us guidelines for the diagnosis of a viral infection and the consideration of concurrent infections. Mixed viral infections have been reported but a higher level of medical awareness is raised to be alert especially in endemic regions, where diagnostic dilemmas, complications, unnecessary expense of resources and prolongation of the course of the disease can be raised.

Key words: *endemic, tropical, viral, febrile illness, infections.*

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INTRODUCTION

Viral diseases are a huge burden for the population, in addition to representing the main cause of morbidity and mortality due to infectious diseases worldwide.

The first viruses were described at the end of the 19th century, being the first to be discovered the tobacco virus, later it was discovered how they infected cells and tissues, then it was possible to differentiate the viral affections and finally the treatment and pathogenesis of them. And so, over several decades, even today, the scientific process continues to grow, expanding knowledge, in addition to the development of vaccines

Viral infections caused by dengue generate asymptomatic disease, classic disease and the severe form or dengue hemorrhagic fever. The virus attacks both macrophages and Kuppfer cells, generating an elevation of transaminases, considered a hepatotrophic virus, as well as the hepatitis A virus causing the characteristic inflammation of the liver.

The majority of viral diseases present similar conditions, so it is difficult to establish a specific diagnosis, mainly in the prodromal phase that presents with fever, headache, myalgias, which accompany multiple symptoms. For this reason the diagnosis requires laboratory confirmation.

The diagnostic strategies depend on the evolution of the disease and its stage. Most of these have three phases that are characterized by a feverish onset with chills followed by a critical phase and the convalescence period in which clinical improvement is observed and laboratory tests take time to normalize. During the first period techniques are used to detect viral nucleic acid because it is the moment of its replication and maximum viremia levels begin, however there is a window period in which the virus is undetectable, so in this subacute

phase, IgM antibodies are detected. Finally in the last phase, seroconversion is detected, that is, the phenomenon in which IgG antibodies are raised.

Following is a clinical case of dengue in conjunction with hepatitis A, mixed patterns of infections have been reported. However, these cases are underdiagnosed, this is why it is considered an issue of importance for the development of health professionals.

CASE PRESENTATION

A 36 year old woman presented to the emergency department of a private hospital in Quito, capital city of Ecuador, during the summer with fever, myalgias, leukopenia and elevated aminotransferase levels.

Two weeks before presentation she was working at the Amazon region. She has been there for ten days, during which she didn't present any discomfort. When she came back, she began to feel a nonspecific progressive malaise along with fatigue and chills. The patient took acetaminophen to alleviate her symptoms. After, approximately, 3 days fever occurred (with temperatures as high as 40 degrees) along with myalgias, and abdominal pain. Despite the administration of acetaminophen, the fever persisted. After two days, the patient sought medical attention at an urgent care clinic. At the night she began with diaphoresis.

At the physical examination, her temperature was 39,5 °C and laboratory test results were notable for a leukopenia count of 3200 per cubic millimeter (reference range: 5000-10 000) also aminotransferase levels TGO and TGP were twenty times beyond the upper limit. (745 and 742 U/L respectively) (Reference range from both: 38 U/l). She was admitted for further evaluation and symptom relief.

In the emergency department, a review of systems was notable for the presence of fever during five days of evolution. Additionally, she presented anorexia and abdominal pain during three days along with myalgias and a characteristic retroocular pain. The patient had no weight loss, neither bleeding, diarrhea, vomiting, nor other gastrointestinal, neurologic or genitourinary symptoms. She reported no contacts with sick persons, although she reported a journey to the Amazon region during 10 days, two weeks ago.

She said that she went there once a month and had no experienced these symptoms before. She had no notable events in her medical history except for a familial history of rheumatoid arthritis (father and grandmother). Her last menstrual period was three weeks before presentation, she reported sexual activity with use of condoms with only one sexual partner. She took no medications and had no known allergies.

She worked as a project manager in the Amazon for approximately one year, she went there every month during 10 days. She lived in a sunny area in Quito, and in a hut near a lake in the Amazon region. She is sedentary and vegetarian for approximately 10 years. She had a house cat that was permitted to go outside, and a lot of birds, monkeys and flies in the area of the Amazon where she worked. There was no history of use of tobacco, but she used marijuana twice a month, and alcohol socially (two times per month).

On examination, the temperature was 39,5 °C, the blood pressure 120/78 mm Hg, the pulse 98 beats per minute, and the oxygen saturation 92% while the patient was breathing ambient air. The patient was described as appearing well. There was no icterus, no cervical, supraclavicular, axillary or inguinal lymphadenopathy. Cardiac examination reveal a tachycardic rhythm, with no murmur. Additionally, neurologic examination was normal. Abdominal examination revealed a mild pain in the upper right quadrant, peritoneal signs along with Murphy sign were negative.

On the other hand, an ultrasound of the abdomen and pelvis was normal, and her electrocardiogram was also normal. Levels of creatinine, prothrombin time, partial-thromboplastin time were normal. Malaria test was negative. Test for hepatitis A and Dengue IgM were positive. Transaminases were elevated 20N beyond the upper limit and a mild leukopenia was noted. Other laboratory test results are shown in Table 1.

Samples of the urine were obtained for culture purpose and normal saline was administered intravenously to prevent dehydration due to fever. Diagnostic test were performed and then she was hospitalized.

Variable	Reference Range Adults	This Hospital, On presentation
Hemoglobin (g/dl)	13.5-17.5	14.7
Hematocrit (%)	41-53	42.1
White cell count (per mm^3)	4400-11 000	3200
Neutrophils (per mm^3)	2000-8000	2491
Lymphocytes (per mm^3)	1000-4400	401
Platelet count (per mm^3)	150 000-450 000	184 000
Creatinine (mg/dl)	0.50-1.20	0.67
TGO (U/L)	10-38	745
TGP (U/L)	10-38	702
Total Bilirubin (mg/dl)	0.20-1.30	0.58
Direct Bilirubin (mg/dl)	0-0.40	0.26
Indirect Bilirubin (mg/dl)	0-1.10	0.32
PCR (mg/L)	0-10	27.80
Dengue IgM		Positive IgM, IgG Negative
Malaria Immunochromatography		Negative
ANTI HAV IgM (ELISA)	<0.4	0.56

Table 1. Laboratory Data

Differential Diagnosis

This relatively young and otherwise healthy woman presented symptoms of fever, myalgias and clinical signs that included mild leukopenia and elevated aminotransferase levels. She had no important findings on her skin that could have represented a wound from an insect bite.

The hemogram was remarkable by the finding of leukopenia with no thrombocytopenia nor anemia. Finally, she had elevated aminotransferase levels with no hyperbilirubinemia. Although, the combination of fever and the travel history is highly suggestive of an infectious process, other potential noninfectious causes should be considered.

Noninfectious Causes.

A hematologic malignancy, acute leukemia, could explain this patient mild leukopenia, although leukemia can occur with variable number of leukocytes. Chronic leukemia always occur with leukocytosis. However, all the other hematologic lines are in normal ranges, there are no cytopenias that indicated a bone marrow failure, so this diagnostic was less probable. In the same way, symptoms in this patient developed rapidly, and an indolent presentation is expected with cancer. Also, in the physical exam no adenopathies were seen, and no ecchymosis were noted. (Kobayashi & Weil, 2018).

CRP, an acute phase reactant, is also elevated in this patient. CRP is a protein that is a member of pentraxins, molecules that act in the innate immune response, its particular role is the ability to bind to phosphocholine, and this allows elimination of foreign pathogens and recognition of phospholipid contents in damaged cells. It can also activate the complement system, which can worsen tissue damage in some cases. It is not specific of an inflammatory or infectious process, however, it can reflect the presence and intensity of one of them. (Kushner, 2017)

The CRP level of 27.80 is mildly elevated, which is more consistent with an infection, values over 50 mg/dl are strongly associated with bacterial infection, lower degrees are associated with viral infections, as seen in this patient. (Irving, 2017). In malignancies it has a prognostic factor, also it can distinguish between a clonal or reactive process. In this case the patient didn't have the presence of blasts in peripheral blood, which excluded hematologic malignancy. (Kushner, 2017)

The patient abdominal pain, fever and elevated aminotransferase levels (20N above the upper limit), fulfill criteria for acute cholecystitis or cholangitis. However, the history of pain in acute cholecystitis is severe and steady, and often there is a history of ingestion of a

fatty food that preceded the pain, in this case there was a history of a trip to the Amazonia before the onset of symptoms. (Zakko, 2018)

In laboratory evaluation, the patient should present with leukocytosis, as a result of the inflammatory process that happens in the gallbladder, also elevation of bilirubin and aminotransferase were expected to see because of the obstruction in the cystic duct. In this case the patient had leukopenia and aminotransferase levels were elevated 20N, which is not usual in these pathologies that reported only mild elevations including in complications. (Zakko, 2018). Also, Murphy sign in this patient was negative and the US was normal so the last one didn't suggest clinical features of acute cholecystitis such as edema of the gallbladder wall. (Zakko, 2018)

This patient could have a disease triggered by a viral infection such as hemophagocytic lymphohistiocytosis, which could be presented with fever, and cytopenias. One of the criteria of this disease, is that the absolute neutrophil count is <1000/micro. In this case, the patient had her neutrophil count in normal ranges. Five of eight criteria should be meet of the HLH-2004 TRIAL to confirm the diagnosis. This patient only meets one of the criteria, which made the diagnosis improbable. (McClain, 2018).

Infectious Causes.

The patient had epidemiologic risk factors that may have anchor to a specific infectious etiology, however the infectious causes are multiple, so constructing differential diagnosis between them would be helpful. Her illness was developed during the summer, and 14 days before it, she was in the Amazon region near a lake with multiple insects. In addition, she had contact with her cat, monkeys and mosquitoes making zoonosis or mosquito-borne infections most likely. (Kobayashi & Weil, 2018)

Could this patient have had malaria, which may be developed after exposure to mosquitoes? Plasmodium are parasites, member of protozoans that are transmitted through the bite of a female mosquito called anopheles. In January 2018, WHO organization reports an increase in cases of Malaria, especially in the Amazon región being in the first place Morona Santiago with 72% of cases due to Plasmodium vivax and only 28% to Plasmodium falciparum. The patient had the history of a trip and exposure in a risky area. (Orbe, 2012)

There are four types of parasites of the human malaria which are: Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malarie. As mentioned above, Plasmodium vivax is the most common type of malaria infection and Plasmodium falciparum causes the most severe form of the disease. (Pinault & Hunter, 2011)

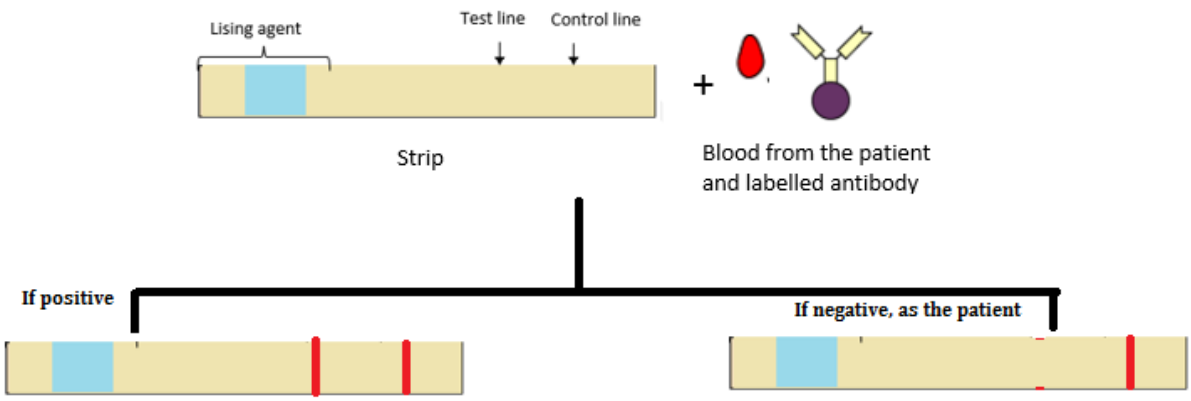
The life cycle of Plasmodium starts with the injection of sporozoites into the human. Then, they replicate into the hepatocytes and evolve into schizonts. The infected hepatocytes breaks and releases merozoites, the form that infects the erythrocytes. The growth of the parasites in the erythrocytes gives rise to successive invasion of merozoites. This cycle takes place every 48-72 hours which leads to an increase in parasitaemia and the characteristic pattern of paroxysmal fever. (Bennet, Dolin, & Blaser, 2015)

This patient presented the classical form of the disease that begins with episodes of paroxysmal chills followed by febrile peaks up to 40 degrees, and later profuse sweating. The patient throughout her hospitalization began to complain about diaphoresis (during night) that could fit with this feature.

However, patients with malaria in laboratory exams present with anemia, thrombocytopenia, elevated aminotransferase levels and creatinine levels. This patient presented an elevated aminotransferase levels and no other alteration, in the case of the malaria the aminotransferase levels rise because of liver failure, and present with more

severe manifestations at this stage such as neurologic findings (altered consciousness), liver failure represents a poor prognosis. This patient was neurologically intact and in the hemogram she didn't has anemia nor thrombocytopenia, making the diagnosis less probable. (Breman & Alilio, 2004)

Finally, the diagnosis is excluded with the rapid diagnostic tests, these are simple test based on antigens with immunochromatographic technology, if the antigen (protein) is presented in the blood sample, the specific antibody will bind it, and a line will be seen. (Hopkins, 2018). These rapid diagnostic tests has a sensitivity of 93% and specificity of 98%, in this patient the test was negative, excluding malaria, as the cause of her symptoms. A graphic of the technique used for this diagnosis is seen below.



Graph 1.Immunochromatrography of malaria. Diagnostic test that detects proteins via a labelled antibody

. This graph was edited from: Macmillan Publishers Ltd: Nature Reviews Microbiology. Bell D, Wongsrichanalai C, Barnwell JW. Ensuring quality and access for malaria diagnosis: how can it be achieved? Nat Rev Microbiol 2006; 4:682. Copyright © 2006.

Mosquito Borne Infections.

Dengue, chikungunya and zika are mosquito-borne infections, the vector is *Aedes aegypti* or *albopictus,* infected with any of the serotypes that cause the disease. They are associated with poor sanitation and low socioeconomic status. Dengue is an enveloped virus,

with RNA genome and is part of flavivirus family. Chikungunya is an alphavirus with RNA genome, part of Togavirus family. Zika virus is another flavivirus such as dengue with RNA genome. (Ministerio de Salud Publica, 2018)

It is important to consider these zoonosis:

> "Any patient presenting with fever that has developed within 14 days after a brief trip to the tropics or subtropics, including those regions where dengue has not been considered an endemic disease." (Simmons, Farrar, Chau, & Wills, 2012)

Dengue was considered over the other viral diagnostic possibilities, because chikungunya is considered the "stooped walk" remarking the characteristic arthralgia that produces, however dengue is called "bone-breaking fever" referring to the myalgias as seen in this patient. The patient didn't have polyarthralgias so these made these diagnostic less probable. Chikungunya also produces lymphopenia, we cannot exclude these diagnosis completely.

Zika and Chikungunya have overlapping clinical manifestations, although zika presents with conjunctivitis, rash, etc. However, we would consider dengue as it has important epidemiological burden in Ecuador.

Ecuador's Public Health ministry, in the epidemiological report during 2015, reaffirm the circulation of the four serotypes on the dengue virus which increases the risk of epidemics and serious illness. The first infection with any of the serotypes gives immunity for that serotype but no to the other ones, sensitizing the individual to severe dengue during a secondary infection. (Real-Cotto, Regato, Burgos, & Jurado, 2016).

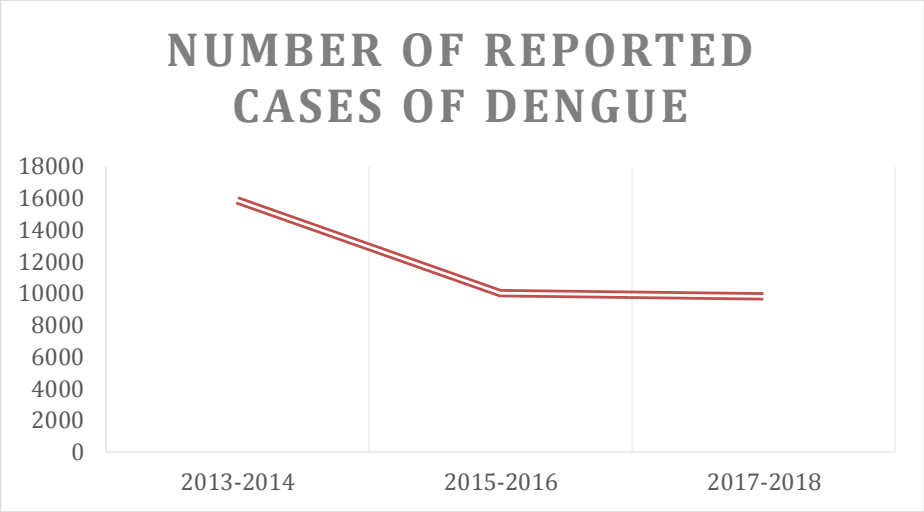
In 2015 the most typeable serotype of Dengue virus in the Amazon region was DEN1 and DEN2. DEN4 was more prevalent in Coast region, where the majority of cases were presented in the period 2012-2013. (Real-Cotto, Regato, Burgos, & Jurado, 2016).

Dengue

Epidemiology.

In the last 50 years its incidence has increased worldwide, it is a major problem of public health. There has been an increasing expansion to different regions and also to the urban zone. During the decade of 1970 in South America, the Andean countries (Ecuador included) carried out a dengue eradication campaign but the surveillance and control measures of the vector were not maintained since then the disease had spread in the form of cyclical outbreaks, especially during rainy seasons. (World Health Organization, 2009).

In 2013, the Ecuador's Public Health Ministry reported an outbreak, there was an increase of reported cases during the first four months of the year, 91% were cases of classic dengue without warning signs and 3% of severe dengue. (Ministerio de Salud Publica , 2013).



Graph 2 Reported Cases of Dengue in Ecuador. (Ministerio de Salud Publica, 2017)

In South America, the vector is present at every country except Chile. In 2016, the majority of cases were reported in Brazil, all the countries reported an outbreak in 2013. (Ministerio de Salud Publica, 2017). Epidemiologic risk factors are multiple such as environmental, human genome mutations, sanitation, mosquito genome, etc. The potential

susceptibility factors for severe dengue are female sex, high body mass index, virus strain, genetic variants of HMHC. (Simmons, Farrar, Chau, & Wills, 2012).

Pathogenesis.

The viral replication process requires an intact host cell, where the virus begins to disamble its genome to synthesize new genome for its offspring. The first step is the adhesion of the virus to the surface of the host cell, which it does by specific receptors. Each virus has a specific target that is the cell by which it has tropism and makes specific connections during the coupling. In the case of dengue, it carries out through the glycoprotein E that binds to specific viral receptors on the surface of the cell (heparan sulfate or lectins). (Bennet, Dolin, & Blaser, 2015)

After binding, the virus must penetrate the cell membrane and lose its envelope, taking advantage of the acidic environment of the endocytic compartment for the expression of glycoproteins required in the fusion of membranes. (Bennet, Dolin, & Blaser, 2015)

The flaviviruses are positive sense RNA virus that replicate itself using the single-stranded RNA as messenger RNA, so the next step is the translation by the ribosomes in the cytoplasm and the result is a polyprotein that is degraded into 3 structural and 7 non structural proteins. The structural proteins are NS-1, NS-2 and NS-3, they generate the viral replication complex. NS-1 is used as a diagnostic tool and a predictor of the severity of the disease. (Bennet, Dolin, & Blaser, 2015)

The host virus interaction depends on the pathogenesis and virulence. Pathogenesis is the phenomenon by which the virus creates a link with its host. Virulence refers to the ability of the virus to produce the disease, it is usually measured as the inoculum, necessary to cause the disease in a susceptible host.

In dengue case, the virus is inoculated directly into the host due to the bite of the vector. Aedes (vector) feeds on a person with viraemia and undergoes extrinsic replication for approximately 7-12 days, then it inoculates the virus in another host by ingesting blood meal. Once the mosquito is infected it will remain with the virus for the rest of its life. Initially, during the first 24 hours a local infection occurs mainly in Langerhans cells and fibroblasts of the dermis. Then, the virus spreads through the lymph nodes or blood approximately 7 days after subcutaneous injection. This viraemia is detectable in peripheral blood at the end of the febrile period. The Kupffer and macrophages cells are the predominantly ones attacked by the virus. (Bennet, Dolin, & Blaser, 2015)

The host's response to infection is part of the innate and adaptive immunity. Antiviral responses are produced with the production of interferon and tumor necrosis factor, responsible for inhibiting viral replication via cell lysis. In addition, the participation of CD4 and CD8 are responsible for producing cytokines and destroying cells infected with dengue, especially the monocytes. (Bennet, Dolin, & Blaser, 2015)

Clinical Manifestations.

The incubation period of approximately 7 days is followed by the sudden start of symptoms. Although most dengue viral infections are asymptomatic, there is a wide range of symptoms that can occur and therefore cause confusion and delay the diagnosis.

There are three specific stages of the disease: the febrile phase, the critical phase and the recovery phase. (Bennet, Dolin, & Blaser, 2015)

The first one is characterized by fever (high as 39 degrees) accompanied by headache, abdominal pain, myalgias, ocular pain, and mild hemorrhagic manifestations such as ecchymosis or petechiae in the skin in areas exposed such as the knees, etc. At the physical exam there should be hepatomegaly, it has to be palpated by the physician below the costal

margin. In laboratory there is a mild thrombocytopenia and leukopenia along with a moderate elevation of the aminotransferase levels. These phase could last for a week and have a spontaneous recovery or progresses into a critical stage.

The patient showed up at the emergency, with those characteristics described above except the skin manifestations, because she had normal platelets as seen in table 1. In the classic dengue fever this sign is not always presented or it could be progressive. Platelets are in low levels, they can be right at the low limit, descend progressively or reach extremely low levels; the last one indicates that the disease will be serious. These patient could have low levels for what she had normally but we wouldn't know without a previous hemogram, however her disease is similar as the classic dengue fever without warning signs. (Simmons, Farrar, Chau, & Wills, 2012)

The second phase, the critical one, is preceded by the end of fever for at least 24 hours. This stage is characterized by an increase in vascular permeability with a plasma leakage (escape of fluids from the intravascular space into the extravascular one), this leads to shock. There is no adequate circulation to the vital organs and therefore a peripheral vascular collapse. Hypotension, tachycardia, hypoproteinemia, ascites, liver failure, somnolence, hemorrhagic manifestations are notable with platelet counts to a nadir of 20 000 per mm^3. (Thomas & Rothman, 2018)

Laboratory findings are remarkable by an increased hematocrit, lower platelet levels and a prolonged PTTa. The clinician must be aware during the 5 and 7 day of illness of suggestive signs of transition to the critical phase instead of the recovery one. These warning signs are persisting vomiting, severe abdominal pain, hepatomegaly confirmed in the US and very painful at the physical examination, mucosal bleeding, lethargy and laboratory signs mentioned above. (Simmons, Farrar, Chau, & Wills, 2012)

These patient, during her evolution at the hospital, has these values of laboratory showed in table 2. She didn't present warning signs, also she was afebrile since her entry at the hospital so ambulatory care was decided.

Variable	At the hospital, Day1	At the hospital, Day 2
Hemoglobin (g/dl)	13.6	13.5
Hematocrit (%)	37.8	39.9
White cell count (per mm^3)	1690	3340
Neutrophils (per mm^3)	637	898
Lymphocytes (per mm^3)	737	1630
Platelet count (per mm^3)	162 000	169 000
TGO (U/L)	1334	1200
TGP (U/L)	1520	1340
Dengue IgM	Positive	--
Anti HAV IgM (ELISA)	1.42	--
PCR (mg/L)	69,30	--

Table 2. Laboratory Data Evolution

As noted before, platelets descended on first day of hospitalization when she was afebrile. The first day without high temperature is crucial so she was in observation for one more day. Her aminotransferase levels were more elevated than the first time, but she didn't show signs of hepatic failure or hemorrhages. On the second day her platelets get better, her neutrophil count was better without risk of a secondary infection and the day before Anti HAV IgM was positive with the Dengue IgM so the diagnosis of a coinfection was confirmed. (Martinez, 2008).

The patient make a transition to the recovery phase spontaneously, she didn't show signs of plasma extravasation. Her hematocrit and platelet count didn't rise or get to extremely low levels, showing a good prognosis. Additionally, the tourniquet test was

negative, no fragility of capillaries was observed and the vital signs were in normal ranges during her hospitalization as seen in table 3. Profound fatigue several weeks after recovery has been reported. (Simmons, Farrar, Chau, & Wills, 2012)

Day of Hospitalization	AP (mm Hg)	Pulse (Beats/min)	RR (Respirations /min)	Temperature (Celsius degrees)	Sat O2 (%)
At her entry	120/78	98	22	39,2	92
Day 1 Morning	100/64	76	20	36,3	92
Day 1 Night	117/80	64	20	36,3	96
Day 2 Morning	105/62	74	20	36.8	90
Day 2 Night	111/76	70	19	37	94

Table 3. Vital Signs

The data in this table was collected from the nursing sheet during hospitalization, with the respective authorization from those responsible.

As observed in table 3, her vital signs were in normal ranges during her hospitalization, including her first afebrile day. A sign of dengue shock is the narrowing of the pulse pressure (a measure of the systolic minus the diastolic pressure) to less than 20 mm Hg. In this case the patient was always over 40 mm Hg. (Simmons, Farrar, Chau, & Wills, 2012)

Diagnostic Tests.

There are two types of tests, the direct ones that detects the viral genome or another components of the virus in the patient's serum and the indirect ones that are based on serology or seroconversion (host response to infection).

The decision of which one to use is based on specificity, time of the illness, and cost. The first ones has high specificity but are costly and must be taken in the time of viraemia of

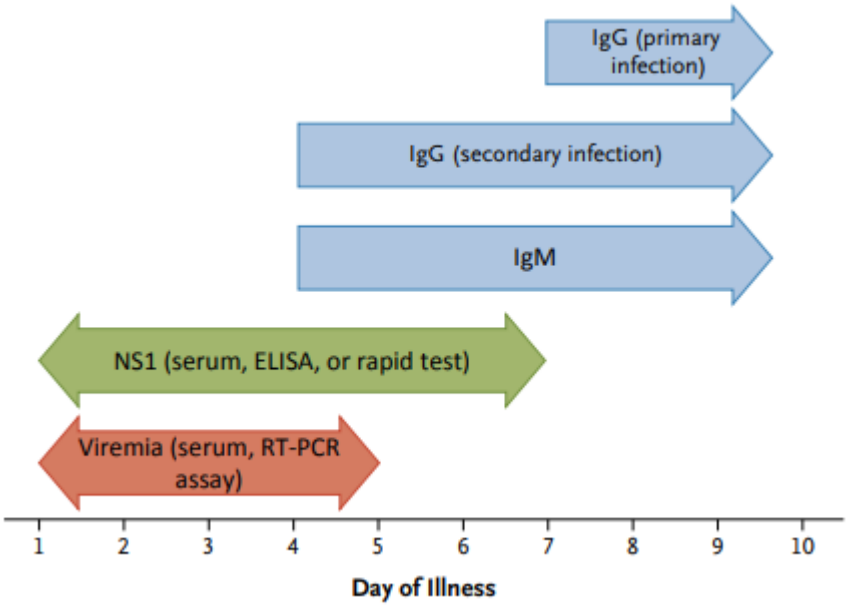
the patient (febrile phase). The second type of tests has a lower specificity but is less costly, the time of the illness is important because there is a window period in which the antibodies are negative. They are specified below in the graph 3.

The technique of choice is the RT-PCR that detects viraemia in all flaviviruses. The recovery of the virus in the blood is achieved before antibodies developed (measured in the indirect tests). It is important to identify the infective dengue serotype for public health, in addition to being a risk factor for the development of hemorrhagic dengue. (Bennet, Dolin, & Blaser, 2015)

Another direct method is the detection of a viral nonstructural protein NS-1, in primary infection the sensitivity and specificity is higher than in secondary infection (90% vs 60%). This reflects a faster production of antibodies in the second time with the same antigen. Recent studies have proven that this protein is present early in the disease, making a viable test of confirmatory diagnosis. (Bennet, Dolin, & Blaser, 2015)

Serologic test are based on the detection of the IgM or paired samples of IgM during the critical and convalescence phase (to prove seroconversion). During the deeffervescence of fever, approximately on the fifth day, there is the peak of IgM which can be detected and it means a presumptive diagnosis. The seroconversion is the confirmatory diagnosis (Fourfold rise in antibody titer). ELISA antibody decapture is superior in specificity against indirect immunofluorescence. Serum IgM declines to undetectable levels within sixty days. (Bennet, Dolin, & Blaser, 2015)

Heterologous reactions with other flaviviruses have been reported in areas where several of them cocirculated and cross-serological reactivity occurs. In South America yellow fever and dengue virus cocirculate with a high degree of reactivity.



Graph 3 Laboratory Diagnostic Tests in a patient with suspected dengue

Graph taken from Simmons, C; Jeremy, J; et al. Review Article NEJM.

Could this patient had reactive hepatitis due to dengue virus?

This phenomenon has been described in a longitudinal study in 37 women who had dengue hemorrhagic fever. A 97,2 % of the patients had fever and orbital pain as the major symptoms. In laboratory findings transaminases levels never exceed 10N the upper limit. Other altered laboratory values showed low platelet counts and elevated hematocrit (75% and 62% respectively).

Sonographic findings showed a hepatomegaly in 90% of the cases. The constellation of signs and symptoms are similar as the anicteric form of the viral hepatitis. It differs from it because the evolution is more variable and has a slightly elevation of the aminotransferase level with the capital sign of hepatomegaly. (Valle & Martinez, 2001).

In this case, the patient couldn't have a reactive hepatitis because her aminotransferase levels were 20N beyond the upper limits. She didn't have hemorrhagic fever and the findings in echography were normal. This is more consistent with a feature of overlapping dengue and hepatitis.

The hemorrhagic dengue fever is a phenomenon in which there is a secondary infection with another serotype of dengue virus. The previously formed antibodies facilitate the entry to the monocytes, increasing the capillary permeability and releasing inflammatory factors that lead to disseminated intravascular coagulation. Our patient had dengue without warning signs, she never presented with symptoms suggestive of hemorrhage.

Faget Sign.

This sign refers to a relative bradycardia when fever is present. When the core body temperature increase as a result of infection, there is an associated increase in heart rate by an average of 8.5 beats per minute for each degree. This sign is specific or can help the physician to narrow the diagnosis into flaviviruses infections, intracellular parasites or typhoid fever. (Mittal & Estiverne, 2015)

The mechanism of this dissociation of fever-bradycardia is not clearly understood but can be related to the cytokines that cause injury to the myocardium or aberrant conduction in the heart. (Mittal & Estiverne, 2015)

In this case, the patient presented with a fever of 39,5 Celsius degrees with a heart rate of 98 beats/ minute. If we consider that for each elevation of one degree then the beats increase 8,5 more times, she had a relatively bradycardia, as shown in table 4 as it was expected.

Temperature (Celsius)	Heart rate (beats/min)
38,3	100
38,9	110
39,4	120
40.0	130
>40	150

Table 4. Hearth rate elevation associated with fever

The information of this table was based on a case report and short review of Mittal; et al, 2015.

Type a Viral Hepatitis

Hepatitis A is a viral infection caused by a Picornavirus, its genome is single stranded RNA, non-enveloped. This property gives them resistance to the environment also preventing them from desiccation and allowing it to survive in acidic environments.

WHO organization in 2016 reported a total of 853 hepatitis cases, 436 due to hepatitis A (more than 50%). The peak of cases was recorded in 2012 probably due to Child's phenomenon. Since this year through 2016 the total number of cases decreased. Fulminant hepatitis happens in less than 1 percent of patients. The association between the lesser number of cases was probably due to the implementation of the vaccine.

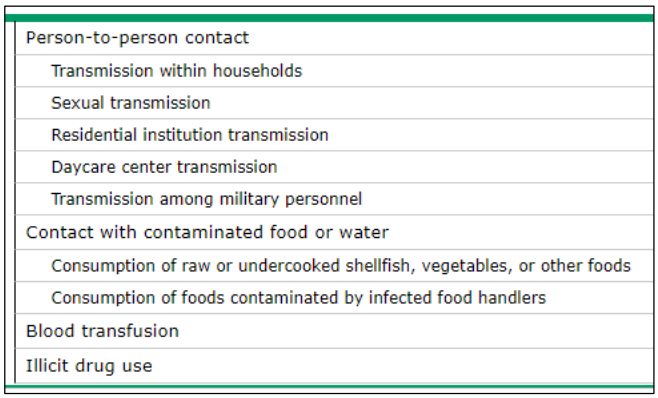
Transmission Routes.

The virus is transmitted by the fecal-oral route and contaminated water causes dramatic spread. After its replication in the liver, the virus is excreted into the bile and reaches higher concentrations in the stool. The maximum period of infectivity is two weeks before jaundice appears or the aminotransferases levels arise. (Bennet, Dolin, & Blaser, 2015)

There is no chronic excretion of the virus, only in neonates that persisted six months after the resolution of the disease. Raw foods have been identified as a source of outbreaks. Also, cooked food could be a source if it is handle by infected people. On the same way, blood transfusions are an unusual cause of transmission. (Bennet, Dolin, & Blaser, 2015)

There are two reported cases of vertical transmission, during the first trimester is associated with intestinal perforation, later, in the third trimester the infectivity is lower, and there are no associated symptoms in newborns. (Bennet, Dolin, & Blaser, 2015)

In 1990 there were reported cases of transmission in drug users, although no new cases were reported since then. The major association was with healthcare and hygienic habits. The following graph summarizes the risk factors for transmission.



Graph 4 Routes of Transmission

This graph was extracted from https://www.uptodate.com/contents/image?imageKey=GAST%2F80824&topicKey=ID%2F2692&search=hepatitis%20a&rank=1~150&source=see_link

Pathogenesis.

Hepatitis A is called the short incubation infectious hepatitis, with a period of approximately four weeks or 28 days. There are three genotypes that infect the human (I, II, III) and they are divided into subtypes (A and B). In this case the only reservoir is the human body. Additionally, the genotype does not correlate with the fenotype, there are not studies that associate certain type of virus with more severity of the disease. The genotype I is the more prevalent worldwide, and the subtype IA is more frequent than IB.

First, the virus is ingested through the mouth and when it reaches the stomach it resists the acidic environment, travel through the gut, via the enterohepatic circulation, and reaches the liver where its replication begins. In the hepatocyte cytoplasm, the virus starts to dissemble its genome, then it is excreted to the sinusoids and hepatic canaliculi. Finally, the virus invades the gut so it is excreted in the stool. (Goldberg & Chopra, 2018)

The host immune response is mediated by cells, especially CD8 lymphocytes and natural killers, both act in the hepatic injury. One hypothesis states that antibodies have the principal role in preventing the spread of the disease, and that the lymphocytes are responsible for the hepatic injury which is consistent with the affirmation that the disease is in fact an alteration of the host's immune response and not due to the virulence of the virus itself. (Lai & Chopra, 2018)

The main anatomopathological finding is hepatic necrosis usually in patches. When there is less than the ten percent of viable hepatic parenchyma, alterations in coagulation are observed. The cells that regulated the clearance of the infected hepatocytes are interferons, principally the gamma subunit, they mediate the immunity, so the host response is less severe. (Bennet, Dolin, & Blaser, 2015)

Clinical Manifestations.

The disease is self-limited and 70% of the infected patients presents with a wide variety of symptoms. The wide range of symptomatology involves since mild discomfort to even fulminant hepatic insufficiency. Like most viral diseases, it has phases. The first one is called prodromal stage, the second one is the critical phase and the latter is followed by the third one, the recovery phase, it can take six months. (Lai & Chopra, 2018)

The prodromal phase is related with the viremia, it last approximately one week and the symptoms are fever, anorexia and abdominal pain. The abdominal pain is localized in the upper right quadrant, it is mild but is aggravated with palpation.

The critical phase happens when the aminotransferase levels are beyond 1000 u/l. The ALT has a peak and it is higher than AST values, due to the hepatic injury. In this phase patients may notice that their urine is darker than usual or that stool has no color. This is due to the elevation of the bilirubin and it is presented with icteric skin. Hepatomegaly is

presented in 80% of cases and is not a sign of severity of the illness. The aminotransferases reach the higher levels one month after exposure, then both are reduced to 75% each week, and they can be elevated six months later. Other laboratory abnormalities include elevation of acute phase reactants and PCR. (Lai & Chopra, 2018)

The recovery phase is spontaneous, and approximately two months after exposure, the aminotransferases values reach levels near normal. Also, signs of jaundice disappear and there is only a mild fatigue during the day. During this phase the physician must do a control of aminotransferases, each month, until the patient reaches the six months. HAV does not become chronic and after the patient recovers from the infection, reinfection is not possible.

Fulminant hepatic failure is the most severe and acute manifestation of the disease, risk factors for this presentation are a preexisting liver disease such as chronic hepatitis B or C, cirrhosis, etc. The laboratory sign that is abnormal and shows a poor prognosis is the alteration of the coagulation time, which indicates that the synthesis of the liver is failing. Clinical symptoms are manifestations of encephalopathy such as confusion, papilledema, etc. The encephalopathy is graded from I to IV, according to specific manifestations showed in table 5. The principal cause of acute liver failure in adults in underdeveloped countries are viral and drug induced hepatitis, whereas in developed countries predominate acetaminophen overdose. (Goldberg & Chopra, 2018)

Grade	**Clinical Manifestations**
I	Mild confusion, sleep disturbance, inappropriate behavior
II	Moderate confusion, lethargy
III	Stupor, slurred speech, motor answer with stimulation
IV	Coma, does not respond to pain

Table 5. Grades of Encephalopathy

Extracted from https://www.uptodate.com/contents/acute-liver-failure-in-adults-etiology-clinical-manifestations-and-diagnosis?topicRef=2692&source=see_link

In this case, the patient presented an elevation of ALT or TGO higher that AST, which is consistent with the hepatic injury of this hepatotrophic virus. Her aminotransferase levels reached a peak, approximately three weeks after exposure, which is consistent with the literature. Also, she presented a prodromal phase that was consistent with viral infections. She never had neurologic manifestations or alteration in her coagulation parameters which exclude a fulminant or necrotic hepatitis. She had the classical form of the viral hepatitis.

Diagnostic Tests.

The diagnosis of acute hepatitis A is confirmed by the detection of specific IgM antibodies in a single serum sample during the acute phase. These antibodies are presented in the initial evaluation and are detectable at the time of the elevation of the ALT. (Lai & Chopra, 2018)

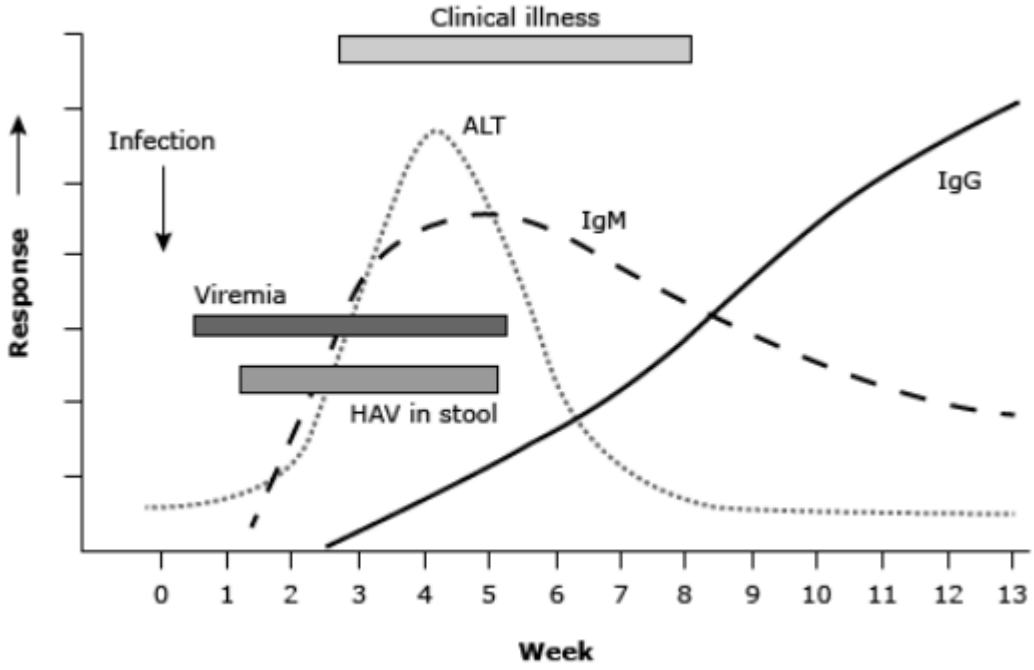
In 10% of patients, serological tests can be negative, if they are performed days after the onset of symptoms, so it is recommended to repeat them if the clinical suspicion is strong. In almost 100% of the patients the IgM anti VHA is positive at least two days after the maximum peak of ALT and can persists during six months.

It is possible to detect HAV viral antigens in stool of the infected patient, one week after the onset of symptoms. In the clinical setting, it is not practical because the patient comes to the urgent care when the viral excretion has finalized.

In the context of research, nucleic acid detection of HAV is used, however it is not approved as a diagnostic tool because it can give false negative results.

The hepatic biopsy is not considered the gold standard because the pathology doesn't give specific signs although portal inflammation is more prominent than with other viruses. The risk of bleeding or complications is higher, so biopsy is not recommended.

The graph below shows the diagnostic tools based on the days after the onset of symptoms.



Graph 5 Diagnostic tools and disease evolution

This graph was extracted from American Medical Association; American Nurses Association-American Nurses Foundation; Centers for Disease Control and Prevention; Center for Food Safety and Applied Nutrition, Food and Drug Administration; Food Safety and Inspection Service, US Department of Agriculture. Diagnosis and management of foodborne illnesses: a primer for physicians and other health care professionals. MMWR Recomm Rep 2004; 53(RR-4):1.

Prophylaxis.

The Advisory Committee for Immunization Practices recommends the hepatitis A virus vaccine for children between 12 and 23 months of age. Vaccination in patients with chronic VHB is also an accepted guideline. Healthcare workers should also receive the vaccine due to the risk of exposure when attending. (CDC, 2007)

CASE DISCUSSION

The initial diagnostic tests in this patient were excluding Malaria, dengue and hepatitis A infection. As explained before any patient with fever and a travel history should be considered for any tropical infections and, in this case, Hepatitis A infection. That is because she was in a place with poor sanitation, where an outbreak of VHA can happen. However, she didn't report any sick contacts that make us think about a foodborne infection.

The serologic test are consistent with a coinfection of classic dengue with hepatitis A, both are hepatotropic virus. However, the initial diagnostic suspicion was only hepatitis A with a false positive result of Dengue. This is why both serological tests are repeated one day before admission, and both results are positive.

The serological diagnostic test for dengue is not the gold standard, because it has a wide cross reactivity with other flavivirus, especially with Yellow fever virus in South America. However, there are not reported cases of a cross reactivity with picornavirus.

There are a few reported cases of concurrent infection of dengue with hepatitis A. The most relevant case was in a 4 year old girl with fever and jaundice. The initial diagnosis was only dengue fever but her aminotransferase levels were 10 times beyond the upper limit so the possibility of coexistent viral hepatitis was raised. In fact she had both infections, her recovery was slower than with only one of this illness, but as soon as the fever disappear on the eleven day she was discharged to home. (Ahmed, 2011)

This is not similar with our patient, she was afebrile by the eight day and she didn't need antipyretics since her hospitalization. When she became afebrile she was in observation one day due to the risk of warning signs, this is a recommendation based on evidence.

Although this patient had the diagnosis of both endemic infections, a detection of nucleic acid was performed and the result became available several days after the presumptive diagnosis was made. The test result was negative for dengue. So the final diagnosis is consistent with the hepatitis A infection, it could be considered the classic form but jaundice never appears. So, maybe the patient has anicteric hepatitis, which is considered more severe, but the patient never presented with stupor or a prolonged prothrombin time that may the physician be aware for a fulminant hepatitis.

Additionally, the patient never had hepatitis A before, so the diagnostic is clearly because a prior infection gives immunity for life. Although, a persistent titer of IgM anti VHA is also an indicator of autoimmune hepatitis. As this is the first time she has this serological test positive she had hepatitis A infection.

So this case shows the false seroreactivity of Dengue, and that indirect methods for detection are lower in sensitivity compared with direct methods. These is a problem because the direct methods are not always available. However, in this infections support management is needed and no specific medications are needed, so the patient evolution was satisfactory. Ten days after her discharge to home her aminotransferase levels were in 530 u/l, which shows that there was a 50% decrease as it was expected.

Furthermore, there are no reported cases of cross reactivity between these two virus, so the patient may have another non typeable flavivirus, but this didn’t change the clinical management.

CONCLUSION

Finally, it can be concluded that the indirect viral detection tests, despite their wide sensitivity and specificity, lack diagnostic value due to the fact that when performing a direct method this is the one that confirms the diagnosis. However, accurate diagnosis is not mandatory to guide the management of these pathologies due to their self-limited nature. A direct diagnostic test was performed given that dengue, being an epidemic disease, these cases must be reported and confirmed. In the case of the patient, the result was negative, which is consistent with the cross-reactivity that occurs between certain flaviviruses. No cross-reactivity has been reported between picornaviruses and flaviviruses, so this could be the first case. Throughout this review process there were difficulties regarding the availability of information, however, sufficient information could be collected.

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