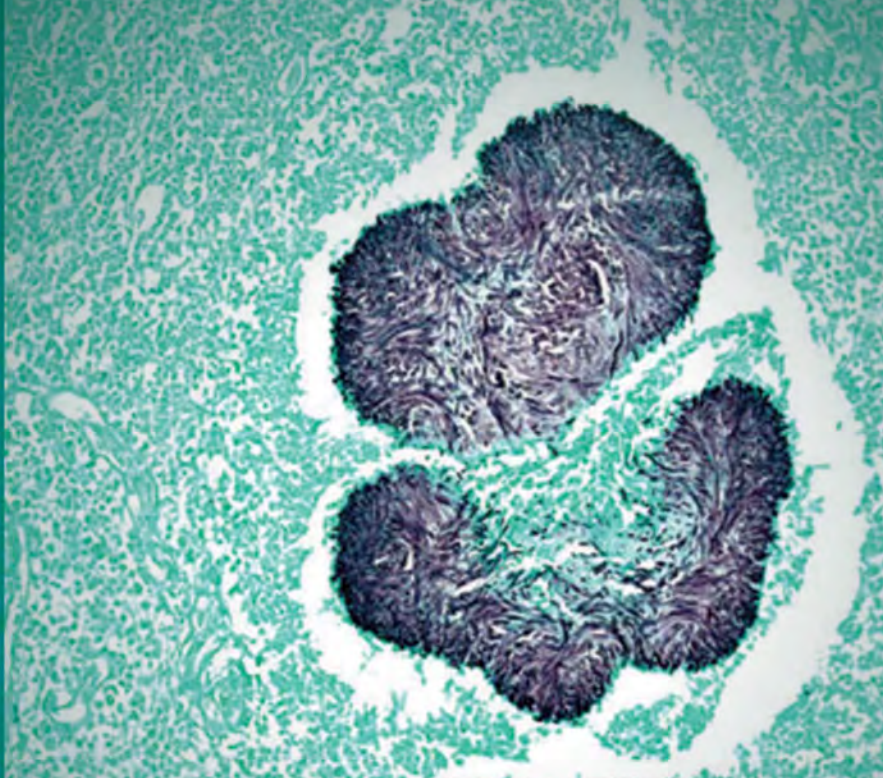



DERMATOPATHOLOGY OF TROPICAL DISEASES

PATHOLOGY AND CLINICAL CORRELATIONS



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Chapter 3 Dengue

Dengue is a disease caused by the dengue virus (DENV), an arthropod-borne virus, or arbovirus, which belongs to the Flaviviridae family, in the Flavivirus genus.[1] The earliest record of a probable case of dengue is detailed in a Chinese medical encyclopedia from the Jin Dynasty (265–420 AD), in which it is referred as a 'poison' associated with flying insects.[2] The disease was also known in southeast Africa, where the Spanish term "dengue" was originated from the Swahili language word "dinga" used in the phrase "Ka-dinga pepo" which means "cramp-like seizure caused by an evil spirit". The slave trade from southeast Africa in the 15th to 19th centuries caused the dissemination of the virus and its vector across America and Oceania, creating world epidemics since the 1780s. In 1789, the American physician Benjamin Rush named the disease 'break-bone fever' and 'bilious remitting fever' during an outbreak in Philadelphia. [2,3]

The dengue virus was first isolated in 1943 by the Japanese physicians Ren Kimura and Susumu Hotta, during an outbreak of dengue in the port city of Nagasaki originating from Southeast Asia during the World War II.[4] The human and zoonotic cycles of DENV is maintained by the blood-feeding *Aedes* mosquitoes, mainly *Stegomyia aegypti* (formerly known as *Aedes aegypti*), a fact that is has been known since 1906.[2] Currently, the dissemination of DENV is a major global public health problem with a particular impact in tropical and subtropical countries, where the warm weather facilitates the growth of the vector in large numbers.[5]

Four distinct serotypes of DENV have been identified (DENV-1, DENV-2, DENV-3, and DENV-4) based on data obtained by neutralization assays.[6] Infection with any of the DENV serotypes may be asymptomatic, or may result in three progressive clinical syndromes, ranging from a flu-like syndrome (known as dengue fever, or DF) to the most severe forms of the disease, which are characterized by vascular compromise (dengue hemorrhagic fever, or DHF), which finally may progress to dengue shock syndrome (DSS).[1,2,6] The co-circulation of different DENV serotypes, and other arthropod-borne viruses that share a similar vector, geographical distribution, and clinical manifestations when infecting humans, makes diagnosis challenging.[7] The most common viruses causing a 'dengue-like' illness are West Nile virus, yellow fever virus, Chikungunya virus, and Rift Valley fever virus.[8,9]

EPIDEMIOLOGY

The worldwide dissemination of the DENV and its vector, *Stegomyia aegypti*, has, over the past 70 years, produced a dramatic increase in the incidence of dengue, especially in areas of Africa, the Americas, Southeast Asia, and the Western Pacific.[1,2,8] In all of these places, thanks to favorable weather conditions (tropical and subtropical climates with average temperatures above 20°C), the wide availability of stagnant water and large populations in urban and semi-urban areas, the virus and its vector have found favorable conditions in which to establish transmission cycles.[1]

Approximately, 2.5–3 billion people, or 40% of the world's population, are at risk for DENV transmission.[9,10] This scenario results in approximately 100 million presumptive cases of dengue annually, with at least 500,000 individuals requiring hospitalization and 20,000 deaths, making DENV the most common arthropod-borne viral infection in the world.[11] Factors thought to be responsible for the continuing spread of DENV include rapid urbanization, population growth, an increase in non-biodegradable products that serve as sites for mosquito larvae proliferation, frequent air travel, and global warming.[12]

Regional differences have been reported between Asia and Latin America. In Asia, hospitalizations principally involve children, whereas in the Americas, they also involve adults.[6] Currently, there are no available effective vaccines or antiviral drugs to combat DENV.[6,13] Consequently, control and treatment strategies are primarily focused on supportive care and prevention. Prevention is undertaken by vector control measures such as the use of full protective clothes, mosquito nets over beds, insect repellents in exposed areas, mosquito eradication programs by fumigation and the elimination of stagnant waters.[13]

PATHOGENESIS

The pathogen

Dengue viruses are positive-sense stranded RNA viruses of the genus *Flavivirus*, family *Flaviviridae*. The DENV genome is about 11 kb, which encodes three structural proteins and seven nonstructural proteins (NS). The structural proteins are: the capsid protein (C), membrane protein (M), and the envelope protein (E). The NS proteins are: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5.[1,14] Structural analysis of mature DENV virions has revealed that the virus possesses an icosahedral envelope and a spherical nucleocapsid core. It is divided into four distinct DENV serotypes that can be further classified into different genotypes on the basis of nucleotide variations.[6] Interestingly, several studies have indicated that certain DENV-2 and DENV-3 genotypes, mainly originating in Asia, are more often associated with severe forms of dengue such as DHF and DSS, suggesting a higher virulence for these serotypes.[6] For example, the first outbreak of DHF in the Americas coincided with the introduction of the Asian DENV-2 genotype. In addition, DENV structural differences in M, E, NS1, NS2, NS4B, and NS5 have been associated with differences in virulence.[15] The glycosylation of E and NS1 proteins are important for viral virulence.[14] Infection with one serotype confers lifelong protection against that serotype, with incomplete heterologous serotype immunity that in many case lasts only a few months.[13] In fact, secondary infection with a heterologous serotype is a risk factor for developing DHF/DSS because it triggers an autoimmune pathogenic mechanism which increases the possibility of dengue complications 40- to 80-fold.[10] The reservoir for infection includes both humans and mosquitoes.[16]

Transmission and physiopathology

The transmission cycle is initiated when the female *Aedes* mosquito, mainly *Stegomyia aegypti* or *Stegomyia albopicta* (the Asian tiger mosquito) bites an infected human. Through the bite, the mosquito ingests fluids and blood that contain DENV. Once inside the mosquito, the virus infects the midgut and spreads to the salivary glands, initiating the replication process. The virus is stored in the saliva, and once large amounts of virus are available, the mosquito is ready to release them.[11]

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In a subsequent bite on an uninfected individual, the virus is injected into the bloodstream with spillover into the epidermis and dermis, resulting in infection of Langerhans cells, dermal dendritic cells, macrophages and keratinocytes.[6] The saliva of the mosquito contains the proteins apyrase and sialokinin, which counteract the hemostatic and immune responses of the host.[11] DENV is internalized in the host cells using clathrin-mediated endocytosis.[14] In the mosquito cells, DENV interacts with heat-shock protein (Hsp) 70, and in mammalian cells it interacts with heparan sulfate and Hsp90, as the main receptors.[11,15] Upon internalization, the virus is released from the endosome, the nucleocapsid is then uncoated, and the RNA is liberated. Infected cells migrate from the site of infection to the lymph nodes. In the lymph nodes, DENV infection is amplified and disseminated through the blood vessels, developing high viral loads or primary viremia, reaching target organs such as bone marrow, spleen, liver, thymus, brain, and endothelial cell, resulting in DENV infection.[11] The viral load in the initial viremia correlates directly with the severity of the disease.[6] Interferon produced by dendritic and natural killer cells can destroy large numbers of viruses and produce asymptomatic seroconversions.[14]

Following infection, mononuclear cells are destroyed by apoptosis, while dendritic cells, endothelial cells, hepatocytes and Kupffer cells are stimulated to produce inflammatory and hemostatic mediators.[17] DENV proteins trigger immune activation; NS1 is an important trigger for complement and cytokine activation, mainly IL-6 and IL-8.[17] This leads to enhanced inflammation, resulting in the extensive activation of CD8+ T-cells early in the infection process.[10] As a consequence, higher amounts of cytokines and chemical mediators are released, which results in damage to endothelial cells and subsequent plasma leakage and thrombosis. Cross-reaction of antibodies that recognize the E protein has been shown to bind human plasminogen and inhibit plasmin activity, adding to the pathogenesis of the autoimmunity mechanisms.[18] Depending on the extent of the infection of the stromal cells of the bone marrow and the levels of IL-6, IL-8, IL-10, and IL-18, haematopoiesis can be suppressed, resulting in decreased blood thrombogenicity.[6] The endothelial damage and severe thrombocytopenia result in increased capillary fragility, clinically manifested as petechiae and easy bruising.[13]

DHF / DSS is strongly believed to be due to a 'storm' of IgM and IgG anti-dengue antibodies from new and previous infections, plus inflammatory cytokines and other mediators (e.g. VEGF, VCAM-1, and ICAM-1), which leads to an increased plasma leakage.[6,7] Generally, after a second infection with a different serotype, the heterotypic neutralizing antibodies may enhance the disease, potentiating the autoimmune mechanism.[10] Higher plasma levels of IL-1, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-13, IL-18, TGF, TNF, INF-γ and IFN-α have been found in patients with severe DENV infections, in particular in patients with DSS.[6] This leads to an increased uptake of the virus by monocytes and macrophages, resulting in an amplification of the cytokine cascade and complement activation, which ultimately results in more plasma leakage which is characteristic of DSS, and the hemorrhagic symptoms of DHF.[10] Differences in disease presentation are associated with genetic variations in HLA class I (A and B) and II (DQ and DR), and non-HLA genes (DC-SIGN1-336 and G6PD).[14]

CLINICAL FEATURES

The DENV infection involves three phases:

1. The febrile phase that correspond to DF
2. The critical phase (plasma leakage) where DHF and DSS develop
3. The convalescent (reabsorption) phase.[19,20]

The incubation period for DF varies from 3–14 days.[21] The initial exanthem of DF is estimated to occur in 50–82% of patients, involves the face, neck, chest, extremities and soft palate, and typically occurs within the first 12–48 hours of the onset of fever. Other initial symptoms include:

- Retro-orbital pain
- Dizziness
- Headache
- Back pain
- Gastrointestinal discomfort
- Pruritus, conjunctival injection
- Hepatomegaly, lymphadenopathies
- Splenomegaly
- Weakness[13]

Subsequently, a generalized morbilliform eruption develops, giving the image of 'white islands in a sea of red' due to abnormal hemostasis[21] (**Figure 3.1**). This finding is more often reported among children[20] (**Figure 3.2**). Minor hemorrhagic manifestations may occur in the form of petechiae, epistaxis, and gingival bleeding. A positive tourniquet test is observed in this phase. Typical clinical laboratory findings in this phase include leukopenia, thrombocytopenia, elevated transaminase levels, hemoconcentration, and hyponatremia.[12] DF is generally self-limiting and rarely fatal. Most patients recover without complications around ten days after the onset of the illness. In some cases, vascular leakage is demonstrated by a hematocrit concentration >20%. There are also thrombocytopenic and coagulation abnormalities, producing DHF. Plasma leakage in dengue could lead to volume depletion and/or pulmonary edema. In cases where high pulse rate and a decrease in pulse pressure to ≤20 mmHg are observed, DSS is diagnosed.[13,16] Purpura, epistaxis and gastrointestinal bleeding can also occur. Laboratory investigations in DHF and DSS reveal a thrombocytopenia that may reach levels of ≤20,000 platelets/mm^2, hypoalbuminemia, elevated blood urea nitrogen, hypofibrinogenemia and complement depletion.[1]

DIAGNOSIS

Histopathology

The findings of skin biopsies are non-specific. The most common histologic findings include mild inflammatory cell infiltration comprising histiocytes and lymphocytes with perivascular distribution, and vascular changes accompanied by tissue edema[22] (**Figure 3.3**). Morphologic changes of the endothelium are uncommon: they are seen as swollen or hyperplastic endothelial cells.[15] Spongiosis and dermal edema are occasionally observed. Red blood cell extravasation is common in DHF and DSS.[11] Cells infected by DENV can be identified with monoclonal antibodies by immunohistochemistry and in situ hybridization.[23] Under an electron microscope, the capillaries of the skin show marked distortion with swelling of the endothelial cells, but the blood vessels are not severely disrupted.[14]

Ancillary studies

The definitive diagnosis of dengue is made by serologic testing for the dengue virus specific antibody, or detecting viral RNA through reverse transcriptase polymerase chain reaction (RT-PCR) on the serum of acutely ill patients. ELISA serology can also be performed against dengue IgM.[1,5] Other diagnostic tests include the hemagglutination inhibition test and viral isolation in culture.[1] The isolation of viruses in cells cultures, such as AP-61 or C6/56 cell cultures is only undertaken for research purposes.[1]

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Figure 3.1 A generalized morbilliform eruption develops, giving the image of 'white islands in a sea of red' due to abnormal hemostasis affecting large areas of the body.



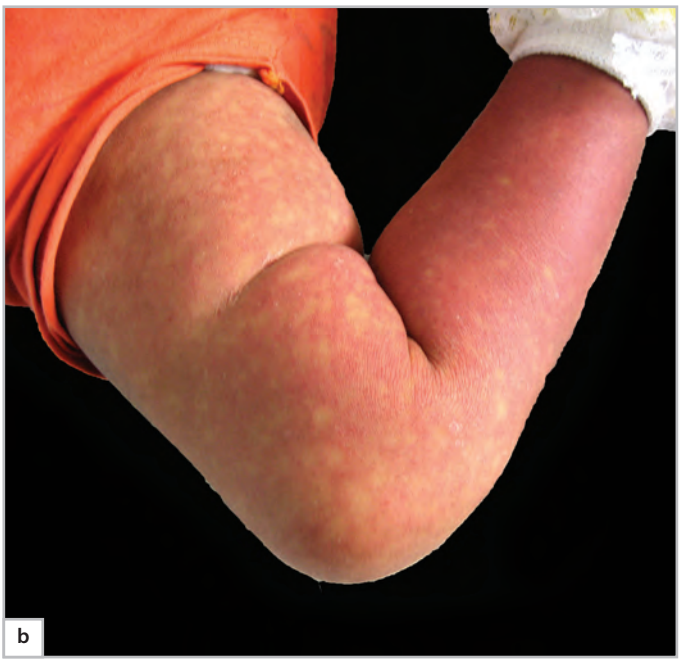

Figure 3.2 Children are more commonly affected by a morbilliform eruption.

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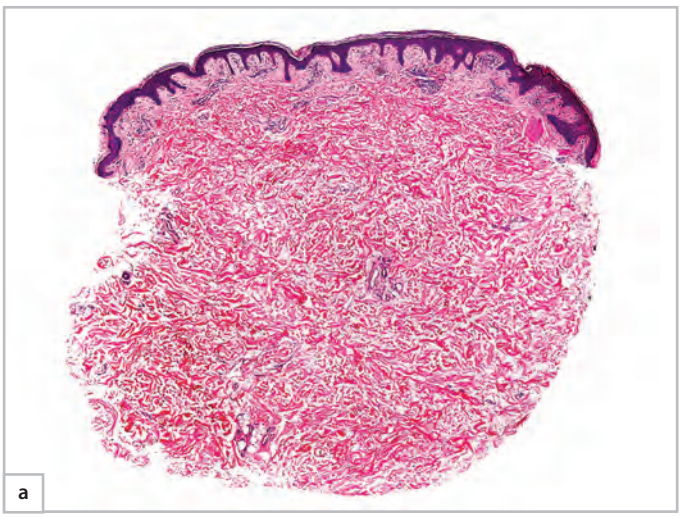

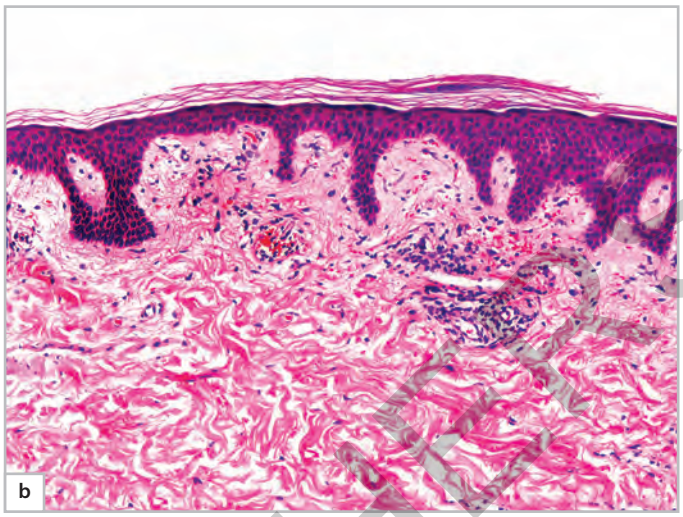

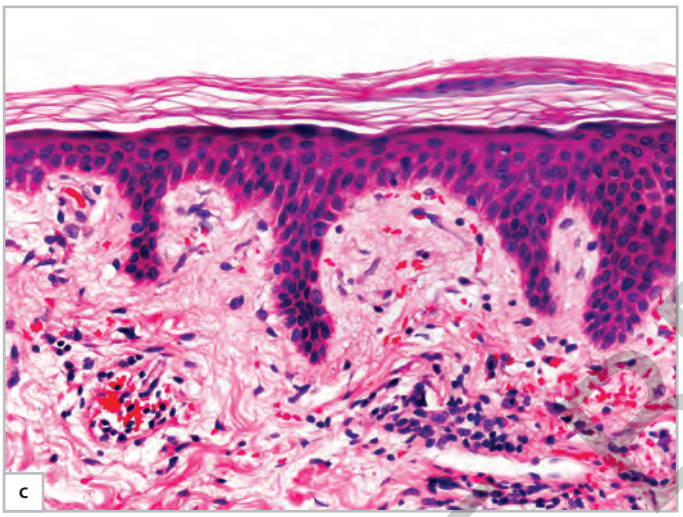

Figure 3.3 The histopathologic features of dengue are non-specific. There are extravasated red cells and sparse inflammatory infiltrates.

PROGNOSIS

Dengue infections are a huge burden on the health systems in tropical countries. Careful clinical examination and rapid diagnostic tests are crucial to early diagnosis. Most cases of dengue resolve with or without treatment. The challenge is to identify the small number of cases where the disease becomes progressively severe and patients could die without appropriate interventions within the first few days of fever. Severe dengue requires early recognition of vascular permeability followed by replacement of fluids to be life-saving.

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DERMATOPATHOLOGY OF TROPICAL DISEASES
PATHOLOGY AND CLINICAL CORRELATIONS

The growth of global trade and travel has not just facilitated human mobility; it has also enabled pathogens and their vectors to spread faster and further than ever before. Increased migration from areas where tropical diseases are prevalent, as well as a higher number of travelers returning from ever more remote destinations, requires heightened vigilance on the part of physicians working in regions where tropical conditions are largely absent.

Although the signs of tropical infectious disease are often visible on physical examination, histopathologic results are also key to the diagnostic process. *Dermatopathology of Tropical Diseases: Pathology and Clinical Correlations* illustrates the dermatopathologic and clinical signs of all the major tropical diseases. Brief descriptions of each entity summarize its epidemiology, pathogenesis and clinical features. Multiple images of the same disease illustrate the range of clinical presentations.

Reflecting the authors' extensive clinical experience, *Dermatopathology of Tropical Diseases: Pathology and Clinical Correlations* is a unique and invaluable resource for dermatopathologists, dermatologists and infectious disease physicians in the developing world, as well as those in developed countries who see tropical diseases in returned travelers and immigrant populations.

- Provides a highly accessible and lavishly illustrated guide to all the major tropical diseases
- Includes almost 600 histologic and clinical images that correlate the pathologic and clinical signs of each condition
- Shows multiple examples of the same disease to illustrate the wide variety of presentations encountered in clinical practice

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