Deep thrombocytopenia due to dengue fever in a patient splenectomized for immune thrombocytopenia

Case report
A 29-year-old woman from mainland France was admitted into the Pointe-à-Pitre hospital, Guadeloupe, in the French West Indies, for deep thrombocytopenia and suspicion of dengue fever (DF). A DENV-1 dengue epidemic was occurring at this moment on the island. The patient’s main medical history was a primary immune thrombocytopenia (ITP) diagnosed 3 years before admission, after investigation of thrombocytopenia revealed by metrorrhagia. The disease was refractory to steroids and IVIG and a splenectomy was performed 14 months earlier. Subsequently, the patient was allowed to stop all medication and her usual platelet count ranged then from 20 to 40 G/L.

She had moved to Guadeloupe 2 months before admission. Two days earlier than the admission, she developed fever up to 38.8 °C associated with headache, retro-orbital pain, diffuse myalgias and arthralgias. Biological diagnosis of recent DF was confirmed with positive NS1 antigen and negative IgM and IgG anti-dengue antibodies. On day 1 of onset the symptoms, her platelet count was 10 G/L with no hemorrhagic sign. On day 2, a mild petechial purpura appeared on the legs and hemorrhagic bubbles on thighs and oral mucosa as well as macroscopic hematuria. Her platelet count dropped to 2 G/L. She received a first high dose of immunoglobulins (IVIG) (1 g/kg) that resulted in a clinical and biological improvement: platelet count grew up to 18 G/L and hemorrhagic signs started to disappear. On day 6, platelet count dropped down again to 1 G/L without any new hemorrhagic sign. A second high dose IVIG infusion was performed. On day 8, platelet count of 76 G/L and the patient had a complete clinical recovery so she was discharged. No other platelet count was performed because the patient refused to consult anymore, but when calling her 2 weeks later, she related no new bleeding.

Discussion
DF is an emergent mosquito-borne viral disease in tropical areas [1] that could occur in any person, including those with chronic thrombocytopenia with an increased risk of bleeding. Reports of dengue fever in patients with ITP and/or splenectomy are scarce. After exhaustive research, only three cases of dengue in patients with ITP were identified (table 1, see supplementary material). The first one was a case of dengue fever with mild hemorrhagic signs in a patient in Mexico, splenectomized for an ITP [2]. He improved with high doses of corticosteroids. The second case was described in Guadeloupe, like the present case, in a patient with DENV-2 DF with deep thrombocytopenia and severe hemorrhagic signs complicating splenectomized ITP with no effect of intravenous IVIG infusions and megadoses of steroids. The case was severe but the patient improved slowly after platelet transfusion [3]. A third case described a transient increase in platelet count after a classic DF in a patient with ITP in Cuba [4]. Thrombocytopenia of moderate degree is a usual finding associated with DF and occurs in 26 to 50% of classical picture in adults [5]. Nevertheless, deep and rapid decrease in platelet count is one of the main criteria for severe dengue [1]. Although poorly understood, several immune mechanisms are implicated in the thrombocytopenia as early bone marrow suppression and immune-mediated destruction of platelets as well as dengue virus-induced vasculopathy and coagulopathy. Furthermore, there is very little correlation between thrombocytopenia and the occurrence of severe bleeding in dengue patients [6]. Studies evaluating the treatment of thrombocytopenia in DF and dengue hemorrhagic fever (DHF) are scarce and therapeutic options are few. There is a limited evidence base for the benefit of corticosteroids in DF. Most of the studies so far have been conducted in children with shock syndrome and have shown conflicting results about possible benefits and adverse effects of them on thrombocytopenia and bleeding [7]. A case-control study testing the interest of high doses of IVIG showed no significant difference concerning the platelet count evolution and the adverse events [8,9]. Another case-control study conducted to test anti-D immunoglobulins in patients with DHF demonstrated a trend but no significant difference in increasing platelet count among those patients [10]. At last, prophylactic platelet transfusion was ineffective to avoid bleeding for severe thrombocytopenia in adults with acute uncomplicated DF [6]. The WHO 2009 guidelines for diagnosis and management of dengue do not recommend...
any of those therapeutic options in case of hemorrhagic complications in dengue [1]. In case of deep thrombocytopenia, strict bed rest and protection from trauma must be respected to reduce the risk of bleeding. Red cells transfusion must be required if severe bleeding is suspected or recognized. Immune thrombocytopenia is an acquired immune-mediated disorder characterized by isolated thrombocytopenia and the absence of any obvious initiating and/or underlying cause of the thrombocytopenia [11]. It is a rare disease with an overall incidence ranging from 1.6 to 3.9 patients per 100,000 person-years. Mechanisms of thrombocytopenia in ITP are complex associating increased platelet destruction mediated by antibodies, impaired platelet production and T cell-mediated effects [11]. First line therapies for the treatment of ITP include corticosteroids, IVIG and intravenous anti-D immunoglobulins. The platelet transfusion is recommended only in severe cases when the vital prognosis is involved, in combination with IV corticosteroids and IVIG in order to stop major bleeding and threatening. However, platelets transfused are doomed to a fast peripheral destruction. The consequence of the splenectomy in the patient of the present case is difficult to determine. The spleen is a large lymphoreticular organ that plays an important role in the defense against many infectious agents but its role against dengue virus remains unclear. Splenectomy might modify the course of DHF and is generally associated with non-severe form of the disease as seen in several cases of dengue fever in patients splenectomized thalassemic children in Thailand and India (table I, see supplementary material) [12,13]. Some authors hypothesize that the absence of splenic macrophages, cells possibly implicated in the pathogenesis of severe dengue, might explain a certain protective role of splenectomy against dengue virus [13].

In the present case, we describe a likely primary DENV-1 DF, although the RT-PCR was not performed, because this was the main virus responsible for the epidemic of the year of the admission in Guadeloupe and the patient recently arrived from France and had never lived in tropical areas. Despite the deep thrombocytopenia, delivering a prophylactic treatment was questionable because the patient presented only mild hemorrhagic signs. Nevertheless, although ITP is not included in the WHO 2009 list of patients at risk of major bleeding [1], we considered the patient at high risk of severe bleeding complications because of the addition of the hemorrhagic mechanisms of dengue and ITP. Furthermore, the history of a severe case in the same situation in the department a few years ago prompted us to great caution [3], without waiting for the classical expected spontaneous rising of platelet count on day 7 [1]. In the absence of recommendations and evidence concerning thrombocytopenia during dengue and ITP, IVIG were chosen because of the history of corticosteroids resistance. Two IVIG infusions were necessary to obtain high and persisting increase of the platelet count and avoid more severe hemorrhagic complication of the critical phase.

Considering the extension of DF worldwide, it may become more frequent in patients with chronic thrombocytopenia, such as ITP. Thus, add chronic thrombocytopenic diseases as ITP to the WHO 2009 list of patients at risk of major bleeding because of the addition of thrombocytopenia and bleeding mechanisms of both diseases might be discussed. Thus, patients with chronic thrombocytopenia living in dengue endemic regions or traveling to such areas should be warned of this risk and may strictly apply prevention against DF. In cases of suspected dengue, physicians should perform a close monitoring and evaluation of the benefit of IVIG or corticosteroids in particular if deep thrombocytopenia and/or hemorrhagic signs appear. On the contrary, no special recommendations might be made to patients with splenectomy, as it seems to have a protective role against DF.

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Supplementary material available on La Presse Médicale website (www.em-consulte.com/revue/lpm)
- Published cases of dengue fever in patient with immune thrombocytopenia and/or splenectomy.

References
Adénopathie sus-clavulaire chez une patiente porteuse de prothèses mammaires PIP

A sus-clus­va­li­ca­ure adney­pathy in patient with PIP breast implants

La présence d’un ganglion palpable, même infracentimétrique, dans le creux sus-claviculaire est toujours considérée comme pathologique. Si à gauche on évoque d’emblée une tumeur abdominale ou pelvienne, à droite on évoque surtout une tumeur intrathoracique. Ces ganglions peuvent également être le siège d’une métastase d’un cancer mammaire ou la localisation d’un lymphome hodgkinien ou non. Une adénite réactionnelle isolée de siège sus-claviculaire est pour le moins inhabituelle.

Une femme de 26 ans a consulté en raison d’une adénopathie sus-claviculaire droite évolutive découverte par l’autopalpation voilà quatre semaines.

On a noté dans ses antécédents la cure chirurgicale d’une hémic-ovaire à l’âge de cinq semaines et un nodule thyroidien gauche de 2 cm, stable depuis trois ans pour lequel l’examen cytologique à deux reprises a affirmé la nature adénomateuse. On a noté des séjours en Océanie, en Asie du Sud-Est et en Afrique Sahélienne il y a un an. La malade recevait 125 µg/j de l-thyroïxine et fumait cinq cigarettes par jour depuis dix ans. Elle possédait un chat qui l’a récemment mordue. Elle a eu une IDR il y a six mois (papule de 7 mm). Elle était apprê-tée et en excellent état général, elle n’avait pas de sueurs nocturnes, pas de signes fonctionnels respiratoires ou digestifs.

L’examen clinique objectivait une adénopathie isolée sus-claviculaire droite de 4 cm de grand axe, mobile, indolore, de consistance ferme et élastique. Les autres aires ganglionnaires cervicales et axillaires ne comportaient que de petits ganglions banals, infra-centimétriques. Il n’y avait pas d’hépatosplénomégalie. On notait des traces de griffures au niveau des deux avant bras, l’examen des seins était indolore et ne montrait pas de masse suspecte chez cette femme porteuse de prothèses mammaires bilatérales depuis huit ans. Le reste de l’examen clinique retrouvait le nodule thyroidien gauche de 15 mm de grand axe, d’allure bancale.

Sur le plan biologique, on notait l’absence de syndrome inflammatoire (VS, CRP, fibrinogène normaux), l’électrophorèse des protéines plasmatiques était normale de même que la NFS qui ne montrait pas d’hyperleucocytose, pas d’anomalies des lymphocytes, pas de mononucléose, pas d’hypér-thyroïdie. On notait un poids déplorable, ni de cholestase, les lactates déshydrogénases (LDH) étaient normales. Les sérologies de la toxoplasmose, de la maladie de Lyme, des infections à virus de l’immunodéficience humaine (VIH) 1 et 2, des infections à herpes virus 1 et 2, du cytomegalovirus (CMV), des hépatites A et C, de la bartonellose, de la fièvre Q, de la syphilis étaient négatives. On notait des ABE témoignant d’une vaccination contre l’hépatite B et la rubéole ainsi que ceux témoignant d’un contage ancien par le virus Epstein-Barr (EBV). Il n’y avait pas d’Ac antinucléaires.

La ponction cytologique du nodule thyroidien n’était pas contributive. L’examen cytologique du ganglion ponctionné à l’aiguille fine a montré un matériel abondant, comportant un fond hématoïde parsemé d’une population lymphoïde gan-