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Hemorrhagic manifestations in primary DENV-3 infection: A case of dengue with warning signs in an adolescent

Davide Mileto [a,d,*], Marta Stracuzzi [b], Alessandro Mancon [a], Erika Naddeo [b], Alberto Rizzo [a], Roberta Caiazzo [b], Federica Salari [a], Margherita Longo [a], Alessandra Lombardi [a], Alberto Dolci [a,c], Vania Giacomet [b,c]

[a] Clinical Microbiology, Virology and Biomergencies ASST Fatebenefratelli-Sacco, L. Sacco University Hospital, Milan, Italy
[b] Pediatric Infectious Diseases Unit, ASST Fatebenefratelli-Sacco, L. Sacco University Hospital, Milan, Italy
[c] Department of Biomedical and Clinical Sciences, DIBIC, Università degli Studi di Milano, Milan, Italy
[d] Institute of Chemical Sciences and Technologies (SCITEC) Giulio Natta, National Research Council (CNR), Milan, Italy

A B S T R A C T

Severe dengue is typically linked to secondary infection. We report dengue with warning signs due to primary DENV-3 infection in a healthy Italian adolescent returning from the Philippines. Severe thrombocytopenia and mucosal bleeding, with clinical and laboratory features suggestive of possible plasma leakage, were managed without shock, highlighting the need for multidisciplinary monitoring and care even in primary dengue.

Dengue virus (DENV) infection is one of the most significant mosquito-borne viral diseases globally, placing nearly half of the global population at risk [1]. In endemic areas, children are particularly vulnerable, and although many dengue infections are asymptomatic or self-limiting, a subset may progress to severe disease characterized by plasma leakage, bleeding, and organ dysfunction [2].

Severe dengue is defined by the WHO 2009 classification as the presence of severe plasma leakage, severe bleeding, or severe organ involvement, and is often associated with a dysregulated host immune response, including increased vascular permeability, hemoconcentration, and circulatory compromise [3]. The WHO 2009 framework also highlights a "critical phase", typically occurring around defervescence, during which plasma leakage can worsen rapidly [4].

A well-recognized risk factor for the development of severe dengue is secondary infection with a heterologous DENV serotype, largely mediated by antibody-dependent enhancement (ADE) [4,5]. Primary vs secondary infection is distinguished serologically: in primary infection, DENV-specific IgM appears first and predominates, while IgG rises more slowly and is initially absent; secondary infection shows an anamnestic IgG response detectable early in the acute phase [4].

In meta-analyses and cohort studies, the relative risk of severe dengue in secondary infections compared to primary is substantially elevated, with estimates suggesting a several-fold increase (approximately 2–7 times higher) [6]. Nevertheless, although rare, instances of severe dengue following primary infection have been documented, particularly in pediatric populations, and suggest that the pathogenesis of dengue severity is multifactorial and not solely dependent on prior immunity [7].

Recent observational studies in pediatric cohorts have sought to identify early predictors of severe dengue. Aung et al. reported that mucosal bleeding, hematocrit rise $\geq$10%, and hypoalbuminemia predicted progression to severe disease in a pediatric cohort along the Thai-Myanmar border [8]. Likewise, Sami et al. observed that early drops in blood pressure, platelet decline, and rising hematocrit were significantly associated with severe outcomes [9].

Despite progress in prognostic modeling [10], there remains a need for high-quality case reports that highlight atypical or exceptional presentations, such as dengue with warning signs occurring in the setting of a primary infection. Such reports enrich the clinical understanding of risk factors, diagnostic challenges, and management decisions in clinical real-life settings.

Here we present an adolescent case of dengue with warning signs occurring in a confirmed primary infection.

A 16-year-old Italian adolescent boy, previously healthy except for retinal detachment surgery at age 14, on 25 July 2025 returned to Milan, after a one-month stay in the Philippines where he had spent a summer holiday in Bulacan province (Central Luzon) visiting relatives and accompanied by family members. This area was among those most affected by the dengue surge observed in July–August 2025, following tropical cyclones.

* Corresponding author. Clinical Microbiology, Virology and Biomergencies ASST Fatebenefratelli-Sacco, L. Sacco University Hospital, Milan, Italy.
E-mail address: mileto.davide@asst-fbf-sacco.it (D. Mileto).

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The Philippines is a dengue-endemic country, with sustained transmission and seasonal peaks typically occurring during the rainy season. In 2025, an increase in dengue cases was reported nationwide, and multiple DENV serotypes, including DENV-3, were documented to co-circulate, contributing to ongoing transmission and recurrent outbreaks [11]. Four days after returning, he developed high-grade fever (up to 40 °C), accompanied by headache, nausea, myalgia localized to the lower limbs, watery diarrhea, and recurrent epistaxis. No episodes of vomiting were reported. Initial symptomatic management at home was unsuccessful, and the onset of petechiae on the lower limbs, which were subsequently confirmed on physical examination, prompted hospital admission on August 2, illness day (ID) 4. The indication for admission was high-grade fever associated with mucosal bleeding (recurrent epistaxis) in a patient returning from a dengue-endemic area. At the time of presentation, the patient did not strictly fulfill WHO 2009 warning signs criteria; however, the persistence of mucosal bleeding in association with the clinical context was considered a relevant clinical concern, supporting admission for close monitoring.

Upon emergency department (ED) admission in a Milan district hospital, the patient was alert and cooperative, oriented to person, place, and time, breathing comfortably on ambient air, and hemodynamically stable with no clinical signs of hemodynamic compromise. No features suggestive of a critical phase with hemodynamic involvement, such as narrowing of pulse pressure, tachycardia with weak pulse, or reduced urine output, were observed during hospitalization. However, the occurrence of recurrent mucosal bleeding requiring intervention represented a clinically relevant complication. Skin and mucous membranes were normally hydrated; no jaundice, cyanosis, or pallor was noted, and there was no cold diaphoresis. Cardiac examination revealed normal S1–S2 with regular rate and rhythm; no murmurs, rubs, or gallops were appreciated, and no pauses or ectopy were observed. Laboratory results at ED admission showed mild leukopenia and thrombocytopenia: WBC 2.4 $\times 10^{\wedge}9$/L (neutrophils 67.3%, lymphocytes 31%), hemoglobin 158 g/L, MCV 86.8 fL, and platelets 101 $\times 10^{\wedge}9$/L (Table 1). As inflammatory markers, C-reactive protein (CRP) was mildly elevated (10.9 mg/L), while procalcitonin 0.27 μg/L. Ten hours later, repeat testing demonstrated further declines in counts: WBC 1.9 $\times 10^{\wedge}9$/L and platelets 75 $\times 10^{\wedge}9$/L, with persistently mild CRP elevation (7.7 mg/L) and a mild isolated AST increase (AST 62 U/L, ALT 20 U/L), while bilirubin remained within the reference range.

On August 3 (ID 5), laboratory findings, including leukopenia and a rapid decline in platelet count, further supported the clinical suspicion and were consistent with early warning signs according to the WHO 2009 classification. In parallel, early changes in leukocyte differential were observed, preceding the subsequent shift toward lymphocyte predominance during the clinical course. The patient was therefore transferred to the Pediatric Infectious Diseases Unit of ASST Fatebenefratelli-Sacco (Milan). On admission the patient was alert, oriented, and hemodynamically stable, with no fever after antipyretics. Physical examination revealed scattered petechiae on the lower limbs. Laboratory tests showed leukopenia and thrombocytopenia (WBC 1.7 $\times 10^{\wedge}9$/L and platelets 31 $\times 10^{\wedge}9$/L), together with mild elevation of transaminases and inflammatory markers. Peripheral smear demonstrated hyposegmented neutrophils and atypical lymphocytes, first identified from illness day 5 and subsequently increasing during the peak of illness.

Given the recent travel history to an endemic area and the compatible clinical presentation, DENV infection was suspected. No dengue vaccination had been administered as well as no reported previous dengue diagnosis.

Microbiological investigations were performed at the Clinical Microbiology, Virology and Biomergencies Unit (CLIMVIB) of ASST Fatebenefratelli-Sacco, a regional reference centre for the diagnosis of arbovirus infections. Within the CLIMVIB arbovirus diagnostic workflow, specimens from suspected cases are tested using in-house real-time PCR targeting Orthoflavivirus RNA alongside validated virus-specific commercial assays (altona Diagnostics - Hamburg, Germany). Although the assays are qualitative, the real-time PCR cycle threshold (Ct) values inversely reflect viral load; for both assays, Ct $\geq$ 45 is set as negative cut-off.

Additionally, virus-specific IgM and IgG are measured by chemiluminescent immunoassay (CLIA) on the VIRCLIA® LOTUS platform (Vircell - Granada, Spain) and reported as index units (index). Results are interpreted according to the manufacturer's instructions: values $<$ 0.9 are negative, 0.9–1.1 equivocal, and $>$1.1 positive. NS1 antigen is measured on the VIDAS® KUBE platform (bioMérieux - France) and reported as index value (negative $\leq$0.99).

Real-time PCR performed on plasma and urine targeting Orthoflavivirus and DENV RNA was positive for both targets, identifying DENV-3, attributed to genotype I and correlated to Major lineage C through the full-length sequence analysis (Fig. 1). Concomitant serology showed IgM positivity (6.6 index) with negative IgG (0.4 index), and NS1 was strongly positive (111.72 index); no prior flavivirus infection or vaccination was reported, and DENV-specific IgG remained undetectable throughout the acute phase, supporting a primary infection (Table 2).

On August 6, ID 8, repeat testing showed rising IgM (17.9 index), persistently negative IgG (0.3 index), continued detection of Orthoflavivirus and Dengue viral RNA in plasma and urine by real-time PCR, and a positive NS1 antigen result (136.85 index), consistent with ongoing primary infection (Table 2).

On the same day, the patient experienced a prolonged episode of profuse epistaxis lasting $>$10 min. Urgent otorhinolaryngology consultation identified an anterior septal varix managed with clot evacuation, nasal packing, and cauterization under local anesthesia. Intravenous tranexamic acid was administered, and due to severe thrombocytopenia, a platelet transfusion was performed, followed by a steady platelet recovery from 31 $\times 10^{\wedge}9$/L at nadir to 237 $\times 10^{\wedge}9$/L on day 3 from transfusion (ID 11) and 402 $\times 10^{\wedge}9$/L at discharge (Table 1).

Table 1
Hematological and biochemical findings over time.

Date	Illness day	Platelets ($\times 10^9$/L)	WBC ($\times 10^9$/L)	Hct (%)	Hb (g/L)	PT (s)	INR	aPTT (s)	Fib (g/L)	ALT (U/L)	AST (U/L)
02 Aug 2025	4	101	2.4	-	158	-	-	-	-	-	-
02 Aug 2025[a]	4	75	1.9	-	-	-	-	-	-	20	62
03 Aug 2025	5	31	1.74	37	130	-	-	-	-	-	-
04 Aug 2025	6	45	3.07	40	139	11.6	1.0	43.3	3.12	26	-
05 Aug 2025	7	45	3.05	43	149	11.0	1.0	42.3	3.41	36	-
06 Aug 2025	8	81	4.18	40	139	10.9	0.9	38.0	3.46	320	653
07 Aug 2025	9	142	5.8	43	150	10.4	0.9	32.4	4.35	466	643
09 Aug 2025	11	237	6.1	41	140	10.6	1.0	31.3	5.18	297	195
11 Aug 2025	13	368	6.3	42	141	10.9	0.9	30.0	5.18	218	101
13 Aug 2025	15	402	5.3	39	135	10.8	0.9	30.2	4.61	136	49

Abbreviations PLT: platelets; WBC: white blood cell; Hct: hematocrit; Hb: hemoglobin; PT: Prothrombin Time; INR: International Normalized Ratio; aPTT: activated Partial Thromboplastin Time; Fib: fibrinogen; ALT: alanine aminotransferase; AST: aspartate aminotransferase.
[a] Follow-up monitoring 10 h after ED admission.

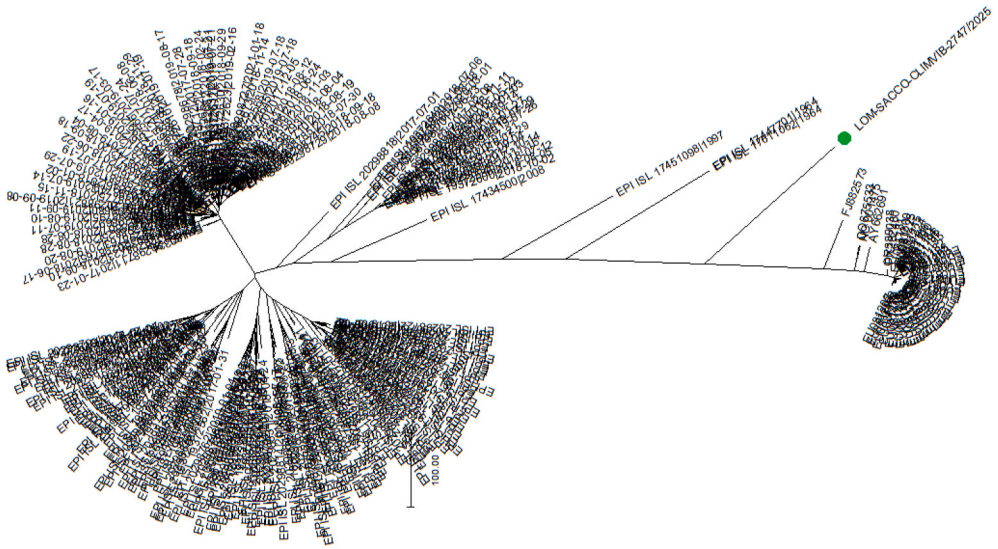

Fig. 1. Phylogenetic tree showing the correlation of case sequence and Orthoflavivirus denguei 3 isolates from NCBI and GISAID
The picture shows how the sequence obtained in this report relates to other of the same serotype, selected on the basis of location in GISAID and highest similarity in NCBI. Our sequence (Green Dot) does not fall into any cluster formed by other ones: included isolates were obtained mainly between 2016 and 2018, thus a significant temporal gap is present, preventing a precise interpretation of the phylogenetic data.

Table 2
Virological and serological findings over time.

Date	Illness day	Dengue virus RNA Plasma (Ct)	Dengue virus RNA Urine (Ct)	Orthoflavivirus RNA Plasma (Ct)	Orthoflavivirus RNA Urine (Ct)	NS1 (Index)	IgM (Index)	IgG (Index)
03 Aug 2025	5	22	32	21	32	111.72	6.6	0.4
06 Aug 2025	8	30	36	27	33	136.85	17.9	0.3
11 Aug 2025	13	37	NEG	NEG	41	0,55	34.3	1.3

DENV: Dengue virus; OFLV: *Orthoflavivirus*; Ct: cycle threshold.

During hospitalization, transient elevations of liver enzymes (AST and ALT up to 466 U/L, subsequently decreased to 136 U/L) and LDH (peaking at 908 U/L, later normalizing to 278 U/L) were observed, while coagulation parameters progressively normalized (aPTT from 1.47 at admission to 1.01 at discharge). Fluid management was conducted conservatively with a restrictive approach aimed at maintaining euvolemia. In parallel, a progressive shift toward lymphocyte predominance was observed, with reversal of the neutrophil-to-lymphocyte ratio as the total white blood cell count recovered.

Defervescence occurred by ID 7. On ID 8, mild pedal edema and a confluent purpuric, vasculitic-appearing rash over the posterior lower extremities emerged, suggestive of possible mild plasma leakage; both regressed spontaneously over the next few days, with concurrent resolution of gastrointestinal symptoms and normalization of oral intake.

On August 11 (ID 13), real-time PCR still detected DENV RNA in plasma at a low level (Ct 37) with undetectable urine DENV RNA while the pan-orthoflavivirus assay was negative in plasma and weakly positive in urine (Ct 41). NS1 had declined to 0.55 index, and serology demonstrated a marked IgM rise (34.3 index) with low-level IgG reactivity (1.3 index), consistent with early convalescence.

The patient was discharged on August 13 in good general condition with resolution of bleeding, edema, and rash. A 20-day course of a topical hemostatic ointment was prescribed, and outpatient follow-up was scheduled with otolaryngology and ophthalmology.

Although the highest risk is traditionally associated with secondary infections due to ADE, pediatric cases of hemorrhagic dengue at first exposure are described and warrant a cautious approach from the initial triage of febrile adolescents returning from endemic areas [2,4]. In this context, management was guided by serial laboratory monitoring as dynamic risk markers (e.g.: platelet decline) [4,7,12].

Here we report a primary DENV-3 infection presenting as dengue with warning signs in an adolescent.

Outcomes were favorable also thanks to meticulous supportive care and targeted nose hemostasis; in line with current evidence, platelet transfusion was reserved for clinically important bleeding rather than used prophylactically. Regarding the microbiological diagnostic tools, the complementary use of real-time PCR performed on different biological matrix, NS1 antigen detection, and the specific IgM/IgG quantification, enabled timely etiologic diagnosis, correct classification as a primary infection, and reliable virologic follow-up, thereby reducing uncertainty around supportive therapy, timing of interventions (e.g., control of mucosal bleeding), and discharge readiness.

In pediatric practice, primary dengue infection, although typically considered lower risk, may present with clinically significant hemorrhagic manifestations requiring active intervention and multidisciplinary management. This case highlights the importance of careful clinical monitoring and timely supportive care even in the absence of criteria for severe dengue and without conclusive evidence of plasma leakage according to the WHO 2009 classification.

Consistent with the recently published WHO Guidelines for the Clinical Management of Arboviral Diseases, the present case is classified as dengue with warning signs. Although clinically significant hemorrhagic manifestations required intervention, no evidence of severe plasma leakage, severe organ involvement, or severe bleeding leading to hemodynamic compromise was observed [13].

Moreover, following primary infection, DENV vaccine should be

recommended, wait at least six months after the initial infection before starting the vaccination series [14].

Management is strengthened by standardized schedules of serial hematologic, biochemical, and microbiological assessments used proactively for prognostication and clinical decision-making. Equally important is a coordinated, multidisciplinary diagnostic workflow integrating clinical and laboratory data to improve diagnostic timeliness, classification accuracy, and the overall safety of the care pathway for suspected dengue infection.

Ethical statement

Written informed consent for publication of this anonymized case report and accompanying data was obtained from the patient's parents.

Data availability

Data can be obtained from the corresponding author upon request.

Approval and informed consent information

Written informed consent for publication of this anonymized case report and accompanying data was obtained from the patient's parents.

Use of artificial intelligence tools

None declared.

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CRediT authorship contribution statement

Davide Mileto: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Marta Stracuzzi:** Data curation, Formal analysis, Investigation, Writing – original draft. **Alessandro Mancon:** Data curation, Formal analysis, Writing – original draft. **Erika Naddeo:** Data curation, Formal analysis. **Alberto Rizzo:** Formal analysis, Writing – review & editing. **Roberta Caiazzo:** Formal analysis, Investigation. **Federica Salari:** Writing – review & editing, Formal analysis. **Margherita Longo:** Formal analysis. **Alessandra Lombardi:** Formal analysis, Writing – review & editing. **Alberto Dolci:** Supervision, Writing – review & editing. **Vania Giacomet:** Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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