Severe Thrombocytopenia in DLMF/Lymphoma Malignant/ITP: Review and Case report: A New WHO Dengue Fever classification beyond DHF

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Abstract—

Introduction: *Nowadays, incidence of Lymphoma Malignant with mortality is high. Peoples and former health ministry of Indonesia, FS, suspect Wolbachia-Aedes aegypti (DHF), but pediatrician thought to DENV-3/-4 secondary heterogeneity infection in endemic DENV -1/-2 in tropical rainforest area.*

Method: *Review the pathogenesis of the two Lymphoma Malignant dead cases report, in association with DENV-3 or -4 as secondary heterogeneity infection in tropical rainforest area, Indonesia.*

Result: *Severity Grade of DHF associated with secondary heterogenous DENV-3 or -4 infections. Conclusion: DENV 1-4 is ss RNA in association with emergency pandemic booster of SARS-CoV-2 which is also ss-RNA virus coated, secondary heterogeneity infection, is in one group with virus which could associated as the caused to Leukemia revealed Immune Thrombocytopenia and other tumor incl. Lymphoma Malignant-non-Hodgkin.*

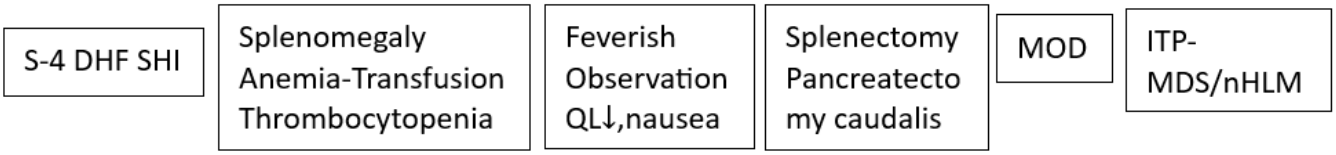
Conclusions: *Ss RNA incl. DENV-4 infection as secondary heterogenous DENV-1/-2 or vice versa, which induce anemia and thrombocytopenia ITP with splenomegaly/Lymphoma Malignant, should be classified to DLMF (grade-4) of DHF classification.*

Keywords— ITP-MDS, Large Granular Chronic Leukemia, Neutrophil Lymphocyte Ratio (NLR), Secondary heterogeneity infection DENV-4, Sepsis, Splenectomy.

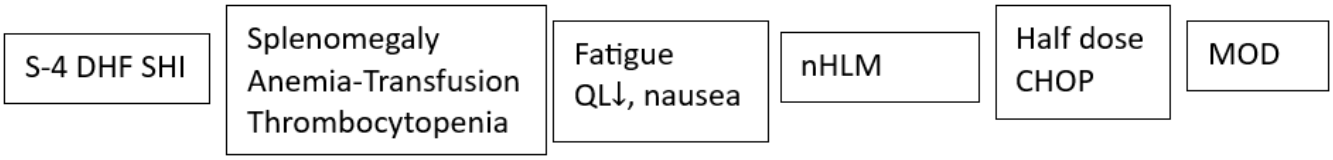
I. INTRODUCTION

Two cases of Acute Lymphoma Malignant mortality in the beginning, and the end of the rainy season in tropical rainforest area (DHF) endemic has shocked peoples in 2024. In Indonesia Aedes aegypti-Wolbachia is spreading in big cities incl. West Jakarta, Surabaya, Semarang and Bali. These two cases are diagnosed in one family. Besides, in the other family, there are also such cases. Number of cases on DENV-3/-4 secondary heterogeneity infection (SHI) 2023 and 2024, and the need of tetravalent DHF vaccine (and no booster COVID-19 AZ due to the recollection from circulation) has been reported in this period, is emphasized not because thrombosis and thrombocytopenia syndrome). AZ pull back the ss RNA vaccine circulation of

COVID-19 all over the world on May 7, 2024 due the asking on March 5, 2024, and loose in court on April 2024 caused of Thrombosis with Thrombocytopenia Syndrome (TTS) as a side effect. SS RNA AZ COVID-19 vaccine, and Serotype-3 or -4 DHF secondary heterogeneity infection, both caused TTS. Most COVID-19 vaccine development efforts aim to activate the immune system against the spike protein (glycoprotein spike on a viral capsid or viral envelope). Pfizer and Moderna have already stopped their mRNA vaccine production since the pandemic COVID-19 is over, which is no longer a pandemic-level threat declared by the WHO May 17, 2023 (while global pandemic was revealed on March 11, 2020). Exactly, the permission to use is only on emergency pandemic conditions. So, there are no causes of Wolbachia and booster COVID-19 vaccine in association with thrombocytopenia and these two Lymphoma Malignant non-Hodgkin cases. The aims of this study are no surgery, and no chemotherapy on severe thrombocytopenia. Many nodules in splenomegaly at the beginning, but the spleen is clear post-op (Fig.1). The liver has supple contour, no hepatomegaly and cirrhosis.



a) Case 1: Healthy Man, 73 y with BPJS (government health insurance) limited therapy



b) Case 2: Healthy Man, 70 y with no limit therapy

FIGURE 1: Dx/ Case 1: Splenectomy & cauda pancreatectomy, 3 days after post-op with never conscious/ wake-up. Macroscopy: Clean of nodules, Microcopy/PA: Lymphoma Malignant; Dx/ Case 2: nHLM and Thyroid Cancer & MOD oedema, dead after 1 week chemotherapy.

1.1 Hypothesis: DLMF caused by secondary heterogeneity infection of DENV ssRNA:

The COVID-19 and DHF, both are caused by viral infection which is well known in Indonesia, SEA. SARS and COVID-19 which attack tractus respiratory, and could be fatal, emerge in China, SARS in 2002, while COVID-19 in 2019. In the early 2020 up to 2023, Indonesia has vaccinated due the COVID-19 pandemic. SARS-CoV-1 is SARS virus, which causes severe acute respiratory syndrome (SARS). SARS-CoV-2 is corona virus, which causes respiratory tract infection of COVID-19. This is the name of the virus, and the COVID-19 is the name of the disease. It is like HIV the virus, and AIDS (Acquired Immune Deficiency Syndrome) as the disease, has been well known. MERS-CoV is a different virus than SARS-CoV2 because of the difference vector, it's by camel, not bird or directly from human to human. DENV 1-4 causes Dengue Fever Classic (DFC), DHF, DHF Shock Syndrome, and DF Lymphoma Malignant (DFLM). DSS due to the endothelial cell's dysfunction (Shock Syndrome) AND Development coagulation disorders induced by thrombocyte/platelet-lymph nodes suppression, where monocytes and macrophages are recruited to replicated.[1] These pathogenesis has not yet associated to Lymphoma Malignant (LM) non- Hodgkin) as the diagnosis of 2 cases report.[1,2] Meanwhile CHOP and R-CHOP are reported successful for the therapy of non-Hodgkin LM in the most endemic area top referral hospital in East Java, Dr. Soetomo General Hospital Surabaya.[2] This inductive phenomena is supported by/ could be associated by Dengue Virus Serotype 4, which is responsible for the outbreak of Dengue in East Java City of Jember, Indonesia.[3] Lymphoma Malignant has been associated with DHF infection.[4,5,6,7].

1.2 DHF, DSS, thrombocytopenia and epigastric pain, and Wolbachia review:

1) Dengue Fever (DF) classic, usually in children have symptoms: fever, headache, nausea vomitus, epigastric pain, muscle joint, rash after the 4th day. On the 4th day is the most dangerous. Dengue symptoms appear 4 to 7 days after the bite of Aedes sp. mosquito.

   DD: typhoid or Upper Respiratory Tract Infection (common cold or staphylococcus).

2) Dengue Hemorrhagic Fever (DHF), DF classic + bruised violet color (arterial damage). Nose, gingiva, or under the skin (petechiae with or without Rumple Leed test)

3) Dengue Shock Syndrome (DSS), a child and adult with plasma is already extravascular due endothelial apoptosis/leakage, blood pressure: 0/0.

4) Lymphoma Malignant Non-Hodgkin (does not contain Reed-Steinberg cells) B in adult: Splenomegaly. Rx/ Cyclophosphamide (Cytoxan) (Endoxan, doxorubicin) are a group chemotherapy which decrease the growth of cancer cells, well known as CHOP regiment with the P for Prednisone.[2]

Thrombocytopenia cut-off: mild 101,000-140,000 per μL of blood, severe |< 25,000 very severe \< 20,000 per μL, moderate 50-100,000/ μL. Thrombocytopenia mild, moderate, severe, critical, and cause mortality is the grade to describe severity score (Table 1). Thrombocytopenia during chemotherapy (Lymphoma Malignant) is often accompanied by a reduction of other blood cell counts.

TABLE 1
CUT-OFF

		Grade I	75-99			**Normal**	2.58
Grade I	>500	**Grade II**	50-74	**Normal**	40-54 M 36-48 F	**Grade I**	>3.68
Grade II	2470	**Grade III**	25-49	**Grade I**	>54 M, >48 F, >44 C	**Grade II**	5.5
		Grade IV	\<25			**Grade III**	7.83
						Grade IV	10.84
a) D- dimer cut-off (ng/mL) N <500 Old age: 90x10		b) Thrombocytopenia cut-off 100,000/µL Successful 16.000 therapy with only NaCl 0,9% is usual in Indonesia		c) Hematocrit cut-off (%)Automated cell counter: Red cell number x MCV (Millions/mm^3 x femto L)		d) NLR cut-off (%)	

TABLE 2
NLR CUT-OFF WAS 3.0. WHO CATEGORIES FOR COVID-19 SEVERITY (ASYMPTOMATIC 1.92, MILD 2.08, MODERATE 4.79 AND SEVERE 9.9 WERE USED

Normal	2.58	COVID-19
Grade I asymptomatic	>3.68	1.92
Grade II mild	5.5	2.08
Grade III moderate	7.83	4.79
Grade IV severe	10.84	9.9

Neutrophil Lymphocyte Ratio in COVID-19 is used for describing prognosis, in DHF for severity score diagnosis.[4]

II. METHOD

Review the pathogenesis of the 2 case reports Lymphoma Malignant, in association with DENV 1-4 secondary heterogeneity infection. First, using Chat-GPT, then Science Direct and other search engines preferred PubMed connection.

III. RESULT

Grade of DHF associated to secondary heterogenous DENV-3/-4 infection

3.1 Two Cases Report mortality of DLMF:

These two dead case reports came from fact and report of the case's subject, family and close friends, doctors, and the author meeting with the patients.

3.1.1 Cases 1 DLMF (HUS):

Man > 73 years, reported DHF secondary infection Aedes Aegypti-Wolbachia area DENV-3/-4, eggs outside the female mosquito doesn't yield (to decrease the population of Aedes Aegypti in his home area). SS DEN-3/-4 secondary heterogeneity induces the development of coagulation disorder[1] (marker: D-dimer). Abdominal pain or tenderness, persistent nausea and vomiting, clinical fluid accumulation: ascites and pleural effusion, mucosal bleed and rash on skin are dubious. Lethargy/faint/tired/apathetic/passive/become slow are dominant. Restlessness is not recorded. Liver enlargement > 2 cm. Laboratory finding of increasing Leukocyte, Monocyte, Lymphocyte and Granulocyte with rapid decrease in platelet count. In 1 month, the fever observed in and out of the hospital due to BPJS patients could not be more than 3 days of hospitalization. At 92 years old, at grandma's birthday celebration, the friendly, polite man steps aside and sleeps again and again (End of July 2023). 2 Sept 2023 HUS came to family lunch but didn't want to eat because of nausea (loss appetite). October still with fever observation with hepatosplenomegaly and cauda pancreas full of nodules by USG, and hospitalized again. His brother is also hospitalized for chronic fever observation but survives by taking Ivermectin. HUS died 6 days post splenectomy and cauda pancreatectomy, on Nov 19, 2023, after 3 months feverish observation with low RBC, thrombocytopenia, and high Leukocyte, hypoglycemia and Hb decreasing and drink plenty of fluids. Epigastric pain, postprandial fullness, upper abdominal bloating, early satiation, nausea, vomiting, lethargic. On Nov 11, 2024, 3 days before splenectomy, he asked for high protein milk low carbohydrate high fat which would make him fit. HUS was Dx/ Lymphoma Malignant by PA Post-op splenectomy and cauda pancreatectomy. Oct 2023, HUS decreased albumin levels were strongly associated with DHF (by meta-analysis of multiple studies, $p<0.05$, while elevated leukocyte Oct 14, 2023. IgG >/ 2.85 IV: Positive IgG antibody to DFV type- 2/4 detected which may indicate a current or past infection. IgG |< 1.64 IV: Negative-No significant level of detectable DFV.

3.1.2 Case 2 DLMF (EeS):

Man 69 years, came to the hospital for BHP medical check-up, go alone with the chauffeur and small luggage, then after 2 weeks Dx/ Lymphoma Malignant with thyroid Ca (T Lymphocyte high production): thymus Dx/ by USG, then were given half dose chemotherapy on 5 May 2024. April 29, 2024 a little bit of moon face. May 3, 2024, couldn't know it was his face. Dead on May 10, 2024 with MOD oedema anasarca.

These 2 cases, endothelial cells dysfunction caused by Imbalance profile of cytokine and other mediators is not reported. Replication phase in hepatocyte and macrophage in spleen, then apoptosis of both supports the diagnosis of Lymphoma Malignant.[1,2,3,5] Differential diagnosis cirrhosis hepatis due hepatomegaly but no varices esophagus, and the liver is supple and soft in case report 1. HUS. Both DLMF cases, never took a bone marrow biopsy because no indication of blast cells in the periphery blood. Spleen and Liver are working extra hard, but not the bone marrow. Suppressed of hemopoiesis especially erythrocyte and thrombocyte, are clinically shown.[1]

IV. DISCUSSION

The author and the whole family are rethinking DHFV-4 because HUS (case 1) loves to go to the garden, his house is at the edge of a rice field, where clean water flood is best habitual for larval mosquitoes of Aedes aegypti. There are so many mosquitos in his house, he got hemolysis, hepatomegaly and splenomegaly. Several times hospitalized, each and every hospitalized person got blood transfusion then the Hb drop again (more frequent transfusion).

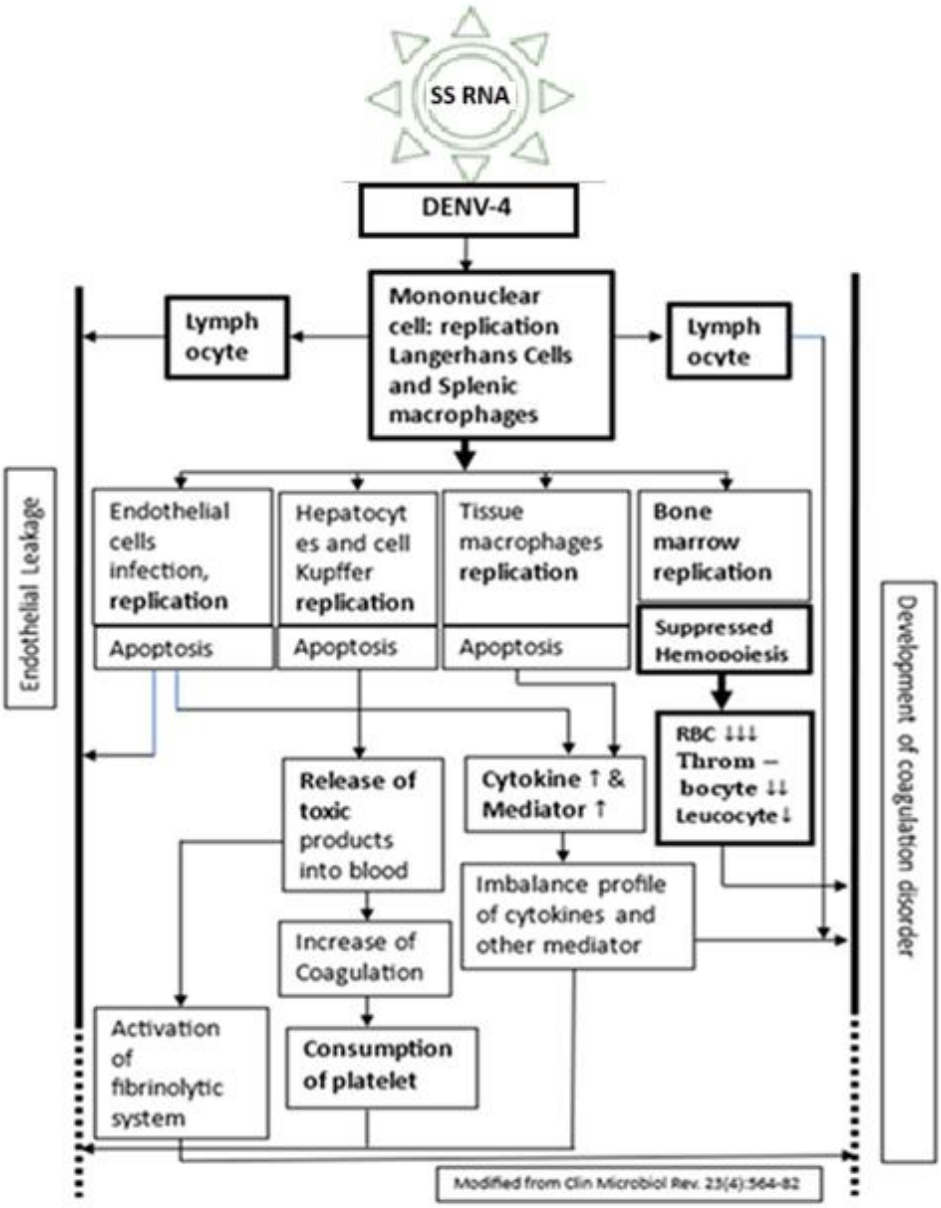


FIGURE 2: Pathogenesis of Lymphoma Malignant non-Hodgkin with drop of Hb and Thrombocyte

Pathogenesis of Development of coagulation disorder (marker: D-dimer) and the endothelial leakage caused by Imbalance profile of cytokine and other mediators in DF, DHF, DSS.[1]

Lymphoma malignant is the Pathologic Anatomy Diagnosis of the splenectomy and cauda pancreatectomy surgery in case 1. LM non-Hodgkin is the chemotherapy diagnosis of case 2. There are also Antibody cross react with platelets and plasmin due to mononuclear cells replications.[1]

4.1 Review cases:

4.1.1 Review Case report DHF, DSS and DEN 1-4:

Pathophysiology all types are the same, DEN Virus (DENV) has 4-5 serotypes. All types are ssRNA virus. So, if someone got DHF, it could be 3 times DHF again. Each person in at risk of dengue fever endemic area, could be 4 times in their lifetime.

Secondary heterogeneity infection is diagnosed by IgG, IgM, whereas **DENV-3** was the dominant serotype (75.9%).[5,6,7,8] Secondary infection with heterologous serotypes is more severe than primary DHF infection, could be explained by IgG for old infection usually DENV-1 or -2, IgM for new infection, usually DEN-3 or -4 in endemic area, tropical rainforest climate.

SS-DENV-3 or -4 secondary infection after -1 or -2, induced endothelial cells apoptosis, suppression hemopoiesis to development of coagulation disorder (increase D-dimer). Lever hepatocytes cells and Kupffer cells replication, necrosis and apoptosis in lever. Splenic and Tissue macrophage replication then apoptosis induced cytokine storm – imbalance profile of cytokine and other mediators. Stimulation B cells and T cells Lymphocytes production (Fig.2). Activation of fibrinolytic system (A) and Consumption of platelets (C). Both A & C induce the development of coagulation disorder (marker: D-dimer)**.**[1] Endothelial cells dysfunction caused by Imbalance profile of cytokine and other mediators.[1]

Review Case report Grade 1: no evidence of bleeding, RL Tourniquet test Positive. Known as Dengue without warning signs.

Review Case report Grade 2: DHF (and Wolbachia). Adult female mosquitos are estimated to be 10 days old, and the lifespan is 14 days. Only the female mosquito could be a vector of DENV. The egg of a female mosquito with Wolbachia couldn't hatch. Known as Dengue with warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increasing hematocrit with decreasing platelets/thrombocytopenia). Evidence of bleeding episodes.

Review Case Report Grade 3: Dengue Shock Syndrome (DSS): presence of weak and rapid pulse rate, low blood pressure or narrow pulse pressure, severe dengue, dengue with severe plasma leakage, where Rx/Albumin is needed. DSS due to secondary heterogeneity DENV-3 infection. whereas DENV-4 occurs at a low prevalence World Wide[6] and spreads the least rapidly.[6] Den-2 has been the most common serotype over the last 50 years. Secondary infection and DENV-3 serotype is most common among dengue patients.[7]

DENV consists of 5 distinct genotypes (I-V). Genotype III is the most widespread and was associated with large outbreaks in Asia, Africa, and America:[8]

DENV-1 and DENV-3 are more pathogenic without immune priming from other serotypes.

Development of Dengue Infection Severity Score is due to thrombocytopenia and leakage of the endothelial cells, and blood pressure/ narrow pulse pressure/ rapid pulse rate, but not in Lymphoma.[4] The DENV also infect and replicates inside a specialized immune cell located in the skin, a type of dendritic cell called a Langerhans cells.[1]

Case report Grade 4 Deadly DLMF: DIC/sepsis (MOD) is when bacteria go inside the blood after post splenectomy or post chemotherapy. And the garden and forest lover only got it although back with antibiotics all the time while needed. Aims: To revised WHO dengue case classification: the system needs to be revised. DENV-4 severity during secondary infection to an antecedent primary DENV-1/-2 infection endemic area. Case DLMF 1 (HUS) only Dx/ by hematology abnormality pre-op, but Dx/ Lymphoma Malignant 3 weeks after Splenectomy and Cauda Pancreatectomy due the extreme drop of Hb and Thrombocyte. Case DLMF 2 (EeS, 70y) only Dx/ non-Hodgkin Lymphoma Malignant (nHLM) & Ca Thyroid by USG (Thymus) before half dose chemotherapy 1 week before mortality. DENV-4 was reported in non-Hodgkin type B with good differentiated (bad prognosis, high grade) vs. poor differentiated (good prognosis, low grade),[2] summons CHOP/ R-CHOP regiment.[2]

CD4+ CD8+ double positive (DP) T cells represent a heterogeneous population. One or more groups of clonal T-cells may be present in a person's lymphocyte population without being considered a lymphoma. Clonal selection of T cells taken place in the thymus and is in charge for producing a useful and functional collection of T cells. The DP thymocytes survive for approximately 3 days previous to undergoing apoptosis (programmed cell death). Splenomegaly and full of nodules, then the fact it is clear and supple post operative describe the process of the apoptosis was seen in case DLMF 1 (HUS, 73y).

In Hodgkin Lymphoma, DNA mutation at B Lymphocytes, and Non-Hodgkin Lymphoma, DNA mutation at B and T Lymphocytes. Case report 2 (EeS) was Dx/ Non-Hodgkin Lymphoma Malignant. He died on 10 Mei 2024.

B Lymphocytes are developed in bone marrow, detect intruder/ attacker and form antibodies to fight infection. After having been stimulated by antigen, B lymphocytes develop into cells producing and secreting antibodies (plasma cells, represent the end-stage of the differentiation of B lymphocytes after their stimulation by antigen). They are thus responsible for the antibody type in the immune response. During development, they are influenced by cytokines and growth factors. And can be characterized according to CD markers (CD19, CD20, CD24, CD72), and presence of immunoglobulins molecules on their outside. T Lymphocytes are produced in thymus. T lymphocytes damage cancer cells and cells which is infected. Th / Treg & effector functions (CD4+), Tkiller Tk and T cytotoxic Tc (CD8+) T suppressor: resulting in osmotic swelling (endothelial cells apoptosis) and following killing and lysis.[4] Th is one of lymphocyte types which help to harmonize immune response so as to approach infection and diseases. In AIDS patients, CD4/CD8 ratio > 1 with CD4 500-1500/mm^3 and CD8 Lymphocyte 150-1000/mm^3, means the immune system is strong and the patients may not have HIV. Case report DLMF 1 (HUS) has

Suppression hemopoiesis due to replication of stromal cells.[1] The author had enough time to think what it should be like, but no behavior representation give assistance to it. Both DLMF cases, the CD4 never deliver below 200 cells/mm^3.

The communication of CD4 with MHC class II greatly become less the number of antigenic peptides required for T cell activation and substantially increases cytokine production by helper T cells.[9] The interaction of CD8 with MHC I can climb up on to a response against pathogens by produce and discharge cytokines and defend from harm of tumors by directly killing transformed cells. Most Tk cells express T-cell receptors (TCRs) that can identify a specific antigen. CD4 cells lead the fight as protection to infections which help Tc/Tk to lyse infected cells. Tk recognizes any infected cell expressing MHC I. Th also helps B Lymphocyte cells to produce highly matured antibodies. Th also encouraging other immune cells, such as macrophages. Both, CD4 (Th) cells and CD8 (Tc/Tk) cells are growth or development different from the common lymphoid progenitor cells in the bone marrow and go on to full grown in the thymus. Low CD4/CD8 ratio reflects increased immune activation and is associated with an increased risk of severe non-AIDS events or cancers. High CD8 count means that the body is effectively controlling the infections. Development always generates more CD4 than CD8 T cells. During a CD8 T-cell reaction to virus infection, there are 3 characteristic phases: a period at the beginning activation and the action of becoming more extensive, a process of becoming smaller of the death phase, and the establishing and maintaining of memory. Memory CD8 T-cell differentiation throughout viral Infection.[1,10] It all needs energy, that's why hypoglycemia and lethargic happens**.**

Neutrophil increase, and Leukocyte decrease. Neutrophil normal 1,450-7,500/μL. In viral infection neutrophil can fall quite low and may stay low for many months. Neutrophil to Lymphocyte Ratio: Normal: 1-2. NLR >3 grade I; < 0.7 Low, mirroring a preserved immune balance. 2.3-3.0 early warning cancer, atherosclerosis, infection, inflammation, psychiatric disorders and stress. High grade NLR narrate bacteria that are already inside the blood vessels. Lymphocyte grow describes viral infection. In both DLMF cases high Lymphocytes have been reported. The NLR cut-off was 3.0. WHO categories for COVID-19 severity (asymptomatic 1.92, mild 2.08, moderate 4.79 and severe 9.9 were used.**[11]**

Hematocrit cut-off >54 Male, 48 Woman, and Rumple Leed and bleeding, none reported in both DLMF cases. Secondary infection and Den-3 serotype most common among dengue patients.[7,8]

4.1.2 SsRNA vs. DsRNA vs. DsDNA, and mRNA:

SsRNA DHF Virus, and also AZ vaccine which is March 2024 recollected from the circulation used for booster. ds RNA or RNAi synthesis to silencing DNA for plant, insect, agriculture and aquaculture. Ds-DNA Wolbachia outside the human body, Adenovirus is one of the DNA viruses.

Messenger RNA (mRNA) is an intermediate which brings genetic information from a gene in the nucleus to a ribosome in the cytoplasmic cell. Transcription is the synthesis of RNA from DNA template where the code in the DNA is converts to a complementary RNA code. Translation is the synthesis of a protein from an mRNA template, where the code in the mRNA is converted into an amino acid sequence in a protein, e.g. spike protein. So ssRNA could be from DHF virus,**[1]** but not from Wolbachia.

TABLE 3
SSRNAV, DSRNAV AND DNAV
1. VIRUS & DISEASE

Virus Name	Disease Name	Contains SS/DS/DNA
SARS-CoV-1 (SARS virus)	Severe Acute Respiratory Syndrome (SARS)	SS RNA
SARS-CoV-2 (corona virus)	breath canal infection of COVID-19	SS RNA
HIV	AIDS (Acquired Immune Deficiency syndrome)	Retrovirus that contains SS RNA
MERS-CoV	Difference than corona virus, Vector: Camel	SS RNA
DENV 1-4	Dengue Fever Classic, DHF, DHF Shock Syndrome, and DF Lymphoma Malignant	SS RNA

MERS (Middle East Respiratory Syndrome)

DENV-3/4 causes: Endothelial cells dysfunction/ leakage (Shock Syndrome) AND Development coagulation disorders (thrombocyte/platelet- LM non-Hodgkin)

2. VACCINE & MANUFACTURE:

Vaccine	Manufacture	Contains SS/DS/mRNA
SARS-CoV-2 (COVID-19)	AZ-Oxford, and J&J	SS RNA spike protein -> B cell used vector adenovirus chimpanzee
SARS-CoV-2 (COVID-19)	Pfizer-BioNTech	mRNA-BNT162b
SARS-CoV-2 (COVID-19)	Moderna	mRNA -1273
SARS-CoV-2 (COVID-19)	Sinovac	Deadly V
DHF Tetravalent (DENV1-4)	Takeda	SS RNA 1-4

4.2 MOD, Endothelial cells dysfunction AND Development coagulation disorders beyond DLMF:

Development coagulation disorders only after post-op (case 1, HUS) and after chemotherapy (case 2, EeS) due to the drop of Leukocytes and T Lymphocyte, Erythrocyte, Thrombocytes, but no report of endothelial cells and development coagulation disorders: Fig 2. Edema anasarca due to multi organ damages (MOD) has been reported in case 2 due to sepsis. Endothelial cells dysfunction AND development coagulation disorders is a good condition to the infection of bacteria into the blood (sepsis) and developed to the end stage known as MOD.

Although live in Wolbachia spreading area Semarang, and Jakarta Barat-Bali, both cases also haven't got ssRNA booster, but high-risk exposure to ssRNA DENV-4 with no IgG and IgM reported. EeS died from MOD post CHOP chemotherapy, also with no endothelial cell's dysfunction and no clinical coagulation disorders. While a long process of fever observation frequently hospitalized since before Sept 2023 and deadly operation of Splenectomy and Cauda Pancreatectomy with 3 days never to wake-up due the knock-down to pain anesthesiology till 19 November 2023. Case DLMF 2 (EeS, 70y) – ssRNA type-4 serologies IgG and IgM were also disregarded, although in Wolbachia spreading area West Jakarta, but no risk of DENV-4. Due to his BHP, fever, and lacking energy, faint and tiredness, EeS has done his demonstration of friendship, and getting in touch with the inheritance, reveals the chronicity of the illness.

Both patients got hepatomegaly and splenomegaly. Case 1 with full nodule in the cauda pancreas, could be due to extreme extra glucose per infusion and per oral. Hypoglycemic is due to replication phase and storm and imbalance cytokine and mediators.[1]

D-dimer cut-off before post op and chemotherapy, increases extremely after post-operation and chemotherapy due to sepsis and the end stage mainly MOD. Thrombocytopenia in the beginning, before operation/chemotherapy, drops at the last days. Decrease Hb in the beginning, before op/chemotherapy, drop at the last days. Hypoglycemia, infused dextrose 5%, extreme glucose per oral, and cauda pancreatomy in DLMF case 1 (HUS, 73y). Ca thyroid diagnosis in DLMF case 2 (EeS,70y), before chemotherapy, is due to the development in thymus,[12] which is normally atrophy in adolescence, which is located in the thyroid area.

Case 1 DLMF (HUS 73 y) splenectomy, and cauda pancreatectomy, 6 days post op Knock-Down due anesthesia pain killer, never wake-up again. When the author asked his sister (Clinical Pathologist) about the argument of hemolysis or for hematopoiesis as the cause of splenomegaly, she didn't give the description of the Blood Smear Morphology-Peripheral. BMP had never been done. And she commented in May 24, 2024 that she didn't know if hemolysis or strong hematopoiesis is the cause of the splenomegaly. He eats dirty street food randomly without any reason, maybe he got chronically poisoned. Sudden splenectomy was indicated by full nodules and quickly dropped the thrombocyte, and cauda pancreatomy by hypoglycemia for 3 months with full nodule on it (Dx/Ca pancreas). He swims 1x/ week, September still swimming, out of first hospitalization also still swimming. Mid November 2023 the last hospitalized, the condition is sleeping all the time, could not open the eyes,

sleepy continuously, difficult to open handphone, then could not open handphone, moreover could not grab the hp, could not self-drinking, could not walk. So, everything drops, Hb, glucose, thrombocyte, while splenomegaly and cauda pancreas increase the size and nodules. It is hemopoiesis due the splenomegaly and also destruction of blood cells, not hemolysis because no shivering was reported. September 29, 2023, he asked to go home, because September 30 he wants to celebrate his birthday. It is all to describe that no one becomes aware of the disease, except it is easy to sleep. Hospitalized not because of fever, or hypoglycemia, or low of Hb, but faint and don't want to eat. Abdominal Pain is a commonly reported symptom in DF.[4,13]

Severe hepatic damage is not common in DENV infections, but elevated liver enzymes suggest that the liver is affected.[1,4] The first diagnosis as cirrhosis has not ever been heard again post operation and post chemotherapy.

Case 2 DLMF (EeS 70 y) got chemotherapy for LGC disorder, 3 days post chemotherapy, lethargy, never talk again. Before the chemotherapy he can contact his cousin indistinctly. On a death case report to the family, a doctor said the thrombocyte become only 200, and could not be saved.

Case 1 (HUS, 73y) 3 months in and out the hospitalized for blood transfusion and hypoglycemic. After 3 months he said Leukemia and severe thrombocytopenia, but then hematology malignancy. PA 3 weeks after Splenectomy and cauda pancreatomy: Lymphoma Malignant.

Case 2 (EeS, 70y) never being hospitalized, come to the hospital himself with fever observation for BHP medical check-up, go out with Dx/ Lymphoma malignant, Ca thyroid with thrombocytopenia and edema anasarca caused by Multiple Organ Damages (MOD).

The thrombocytopenia in dengue is caused by the suppression of bone marrow, platelet destruction by antibodies to the dengue virus, excessive consumption of platelets, viral-replication-mediated destruction of platelets by complement-mediated lysis, and apoptosis.[1,14]

4.3 Comparison Serotype DEN 1-4:

The flavivirus genome consists of ± 11,000bps, which translates into three structural and 7 nonstructural proteins (See "Chimeric virus vaccines"), later. A successful extra valent dengue vaccine should concurrently protect against all 4 serotypes because each person could 4 times be infected by DENV. DENV1-4 have different 3 phases (fever, critical, and recovery), DENV-2 Hemorrhagic critical, DENV-3 Shock Syndrome critical, and DENV-4 have a long recovery phase which could be DLMF. Mutation by DsDNA could be ignoring the stop codon (i.e. UAA, UAG and UGA), which is a generated readthrough mechanism, continuing on that makes a longer string of amino acids. Sometimes this function is combined with the ribosomal frame-shifting to produce an even greater variety of viral proteins.[15] which induced Lymphoma Malignant,[16] which could be by STAT3 mutation,[17,18,19] The global trends in research on endothelial cells and sepsis 2002-2022 has been reported,[20] and the mechanism supported the mechanism in these 2 cases. Wolbachia 16S rRNA haplotypes detected in wild Anopheles stephensi has been reported in eastern Ethiopia,[21] whereas detection of Wolbachia genes in patient with non-Hodgkin's lymphoma already has been set up and reported before.[22] Clinical assessment of dengue and identification of risk factors for severe disease protocol for a multicenter study in 8 countries, incl. hematocrit, white blood cell count, lymphocyte count, thrombocyte count, etc. as well as SGOT/SGPT, plasma albumin etc.[23] Identification of early serological correlates of serious dengue are included, but not yet implicit Lymphoma malignant,[23] although splenomegaly 67% has reported caused by STAT3 -T-Cell Large Granular Lymphocytic Leukemia.[19] STAT3 mutations show the presence of subclinical T-cell clones in a subset of aplastic anemia (AA) and myelodysplastic syndromes (MDS) patients,[24] supported by Lymphotropic virus: chronic inflammation bringing rise of cancer.[25] It seems Adult T-Cell Leukemia/Lymphoma as new biologic insight, and new direction in treatment since 2017 by Mehta-shah, should not be neglected. Prevalence in Indonesia -1 (33.6%), -3 (28.4%); -2(20.5%), and -4(14.9%): 22Oct 2020.[2] Low carbohydrate, high fat, high protein should be given in this early biomarker for prediction of serious thrombocytopenia in DLMF new classification in tropical rainforest area (low- to middle- income countries during epidemics,[27] whereas decreased albumin level was strongly associated with DHF.[27] ITP associated SarCov2 has been revealed.[28]

LIMITATION

This study did not elaborate specifically severe score DENV-1 and DENV-3, which are more pathogenic without immune priming from other serotypes.[4]

It is also recorded unexplained cytopenia in MDS associated with excellence prognosis of Low-Risk MDS without detectable Myeloid-Related mutations.[29] The early detection of DLMF from DF to ITP/MDS/AML[30] and high protein therapy[31] support this study, early mass diagnosis and therapy, but not covered.

V. CONCLUSION

DENV 1-4 is Ss RNA incl. DENV-4 infection as secondary heterogenous DENV-1/-2 or visa versa, which induce anemia and thrombocytopenia ITP with splenomegaly/Lymphoma Malignant, should be classified to DLMF (grade-4) of DHF classification.

Ss RNA incl. DENV-4 infection as secondary heterogenous DENV-1/-2 or vice versa, which induce anemia and thrombocytopenia ITP, then splenomegaly/Lymphoma Malignant, should be classified to DLMF (grade-4) of Dengue Fever classification.

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CONFLICT OF INTEREST

The author declares No competing interests.

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