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The Benefit of DLBS1033 for Deep Vein Thrombosis in A Hemorrhagic Stroke Patient: A Case Report

Association Between Neutrophil-to-Lymphocyte Ratio (NLR) and Dengue Severity in Patients
Treated at Bethesda Hospital, Yogyakarta

hal. 8

A Patient with Non-Hodgkin's Lymphoma of The Spinal Region with Tuberculosis Spondylitis
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hal. 21

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Menimbang Strategi Penatalaksanaan Deep Vein Thrombosis pada Pasien Strok Hemoragik

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Abstrak

Strok hemoragik merupakan kondisi akut dengan tingkat morbiditas dan mortalitas yang tinggi, dan sering disertai komplikasi berupa trombosis vena dalam (*deep vein thrombosis*/DVT). Dilema utama dalam tata laksana DVT pada kondisi ini adalah paradoks terapeutik, di mana penggunaan antikoagulan efektif mencegah embolisme paru, namun berisiko memperburuk perdarahan otak. Pedoman internasional merekomendasikan profilaksis mekanis seperti *intermittent pneumatic compression* (IPC) serta penggunaan antikoagulan dosis rendah pada hematoma yang stabil, meskipun bukti klinis masih terbatas. Alternatif biologis, seperti DLBS1033 yang berasal dari *Lumbricus rubellus*, menunjukkan potensi keamanan dan efikasi pada laporan kasus di Indonesia. Perspektif etika, kebijakan kesehatan, serta inovasi farmakologis dan teknologi kecerdasan buatan sangat diperlukan untuk menciptakan strategi yang adaptif, adil, dan berbasis bukti dalam penatalaksanaan DVT pascastrok hemoragik.

Kata kunci: trombosis vena dalam, strok hemoragik, embolisme paru, antikoagulan, DLBS1033

Abstract

Hemorrhagic stroke is an acute condition with high morbidity and mortality rates, and is frequently accompanied by complications such as deep vein thrombosis (DVT). The main dilemma in managing DVT in this condition is a therapeutic paradox, where anticoagulants use is effective in preventing pulmonary embolism, but carries the risk of worsening intracranial bleeding. International guidelines recommend mechanical prophylaxis, such as intermittent pneumatic compression (IPC), and cautious use of low-dose anticoagulants in stable hematomas, although clinical evidence remains limited. Biological alternatives, such as DLBS1033, derived from *Lumbricus rubellus*, have shown potential safety and efficacy in case reports from Indonesia. Ethical perspectives, health policy, as well as pharmacological innovations and artificial intelligence, are essential to develop adaptive, equitable, and evidence-based strategies in the management of DVT following hemorrhagic stroke.

Keywords: deep vein thrombosis, hemorrhagic stroke, pulmonary embolism, anticoagulant, DLBS1033

Dalam sejarah kedokteran modern, strok hemoragik selalu menjadi tantangan klinis yang menuntut kewaspadaan tinggi. Kondisi ini tidak hanya bersifat akut dan berisiko tinggi, tetapi juga membawa dampak morbiditas dan mortalitas jangka panjang yang signifikan. Salah satu komplikasi paling menonjol yang sering muncul setelah fase akut adalah *deep vein thrombosis* (DVT), suatu kondisi yang diam-diam memperburuk prognosis dan dapat berujung pada komplikasi fatal berupa embolisme paru. Pasien strok hemoragik biasanya mengalami imobilisasi dalam jangka waktu lama, sering kali dengan hemiparesis atau hemiplegia, sehingga memperburuk stasis vena (Kappelle, 2011). Kondisi ini memenuhi kriteria Virchow's triad, yaitu stasis, cedera endotel, dan hiperkoagulabilitas, yang menjadi dasar fisiopatologis pembentukan

trombus. Namun, tantangan terbesar dalam pengelolaan DVT pada pasien stroke hemoragik bukan sekadar jalur patofisiologi, melainkan juga terletak pada paradoks terapeutik. Terapi standar yang digunakan dalam tata laksana DVT pada populasi umum adalah antikoagulan (Greenberg *et al.*, 2022). Penggunaan antikoagulan pada pasien dengan riwayat perdarahan otak, di sisi lain justru dapat meningkatkan risiko perluasan hematoma intrakranial. Dilema ini menuntut bukan hanya pertimbangan klinis, namun juga seni pengambilan keputusan dalam menyeimbangkan manfaat pencegahan tromboemboli dengan risiko memburuknya perdarahan. Perspektif ini meninjau isu tersebut dalam bingkai makro, menghubungkan data ilmiah, pengalaman klinis, refleksi etis, kebijakan kesehatan, serta arah inovasi masa depan.

Epidemiologi DVT pada penyintas stroke hemoragik memperlihatkan bahwa masalah ini bersifat sistemik, bukan sekadar individual. Studi kohort melaporkan bahwa insidensi DVT tanpa profilaksis dapat mencapai 20–40% dalam minggu pertama pascastroke (Greenberg *et al.*, 2022; Kappelle, 2011). Komplikasi yang paling ditakuti, yaitu embolisme paru, meskipun insidensinya sekitar 1% dalam dua minggu pertama sejak onset stroke, namun menyumbang hampir seperempat angka kematian pada kelompok pasien tersebut (Amin *et al.*, 2013). Walaupun demikian, angka-angka tersebut kemungkinan besar masih belum mewakili keseluruhan kasus. Terdapat banyak kasus DVT yang bersifat subklinis, tidak terdeteksi hingga komplikasi embolisme paru terjadi (Amin *et al.*, 2013; Kappelle, 2011). Hal ini menunjukkan fenomena gunung es epidemiologis, di mana kasus yang terdiagnosis hanyalah puncaknya. Dari perspektif makro, fenomena ini memperlihatkan kecenderungan kedokteran modern yang lebih fokus mengatasi kejadian besar seperti perdarahan akut, namun tak jarang masih kurang memberi perhatian pada komplikasi senyap yang memiliki dampak mortalitas tinggi.

Tantangan Konseptual: Antara Trombus dan Hematoma

Secara konseptual, pengelolaan DVT pada stroke hemoragik menempatkan klinisi dalam posisi yang sulit. Di satu sisi, trombosis vena dalam dapat bermigrasi menjadi emboli paru yang fatal, di sisi lain, penggunaan antikoagulan berpotensi mengaktifkan kembali perdarahan otak yang sebelumnya sudah dapat dikendalikan. Paradoks ini berbeda dengan stroke iskemik, di mana antikoagulan justru merupakan bagian integral dari terapi.

Dilema ini dapat dibaca dalam bingkai etika medis klasik, yaitu keseimbangan antara prinsip *nonmaleficence* (tidak merugikan) dan *beneficence* (memberikan manfaat). Pemberian antikoagulan dapat mencegah kematian karena emboli, tetapi juga dapat memperburuk cedera otak. Tidak memberikan antikoagulan dapat berarti menghindari risiko perdarahan berulang, tetapi membiarkan bahaya tersembunyi datang di kemudian hari. Dengan demikian, pengambilan keputusan terapeutik harus senantiasa kontekstual, bergantung pada kondisi pasien, waktu sejak onset, serta hasil pencitraan serial (Greenberg *et al.*, 2022). Pedoman internasional merefleksikan ketidakpastian ilmiah yang masih menyelimuti penatalaksanaan DVT pada stroke hemoragik. American Heart Association (AHA)/American Stroke Association (ASA) menekankan penggunaan profilaksis mekanis segera dengan *intermittent pneumatic compression* (IPC), serta mempertimbangkan penggunaan antikoagulan dosis rendah 1–4 hari setelah onset stroke bila pencitraan menunjukkan kondisi hematoma yang stabil (Greenberg *et al.*, 2022). Rekomendasi ini memiliki level IIb, yang berarti manfaatnya belum pasti. Sebaliknya, pedoman National Institute for Health and Care Excellence (NICE) tergolong lebih konservatif, di mana direkomendasikan IPC dalam tiga hari pertama untuk semua pasien stroke akut yang *immobile*, sedangkan antikoagulan hanya digunakan apabila risiko trombosis jauh melebihi risiko perdarahan (NICE, 2018). Perbedaan arah ini mencerminkan kultur klinis dan filosofi sistem kesehatan masing-masing. Amerika cenderung lebih terbuka pada intervensi farmakologis dengan pemantauan ketat, sedangkan Inggris cenderung lebih konservatif dengan menekankan solusi mekanis. Fragmentasi pedoman ini menegaskan perlunya konsensus global berbasis bukti klinis yang lebih kokoh.

Strategi mekanis seperti penggunaan IPC menjadi salah satu pilar yang konsisten direkomendasikan. Intervensi ini menggantikan fungsi otot tungkai yang lumpuh akibat paralisis. Studi CLOTS 3 menunjukkan bahwa IPC dapat menurunkan insidensi DVT dari 12,1 menjadi 8,5% serta menurunkan tingkat mortalitas dalam periode 30 hari (CLOTS

Trials Collaboration, 2013). Bukti ini memperlihatkan bahwa solusi nonfarmakologis sederhana dapat memberi dampak yang signifikan. Refleksi lebih jauh menunjukkan bahwa kedokteran modern tidak selalu harus bergantung pada intervensi farmakologis. Pendekatan fisiologis sederhana dapat setara efektivitasnya, bahkan lebih sesuai untuk negara dengan keterbatasan akses obat.

Perspektif Farmakologis dan Biologis: Antikoagulan dan Inovasi Baru

Antikoagulan tetap menjadi fokus yang penting untuk didiskusikan dalam tata laksana trombotik vena dalam. Baik *unfractionated heparin* (UFH) maupun *low-molecular-weight heparin* (LMWH) telah lama menjadi tulang punggung terapi, walaupun menimbulkan kecemasan kolektif terkait penggunaannya pada penyintas stroke hemoragik (Prabhakaran *et al.*, 2015). Beberapa studi observasional menyarankan profilaksis *heparin* dosis rendah dapat dimulai sejak 24–48 jam pertama bila hasil CT scan menunjukkan hematoma yang stabil. Namun, bukti-bukti yang tersedia masih tergolong lemah. Di masa depan, perhatian bergeser pada penggunaan *direct oral anticoagulant* (DOAC) seperti *dabigatran*, *rivaroxaban*, dan *apixaban*, yang terbukti memiliki risiko perdarahan intrakranial yang lebih rendah dibanding *warfarin* pada populasi umum (Ruff *et al.*, 2014). Potensi DOAC pada pasien pascastroke hemoragik masih diteliti, namun membuka peluang kompromi terapeutik (Shoamanesh *et al.*, 2025).

Inovasi biologis alami seperti DLBS1033, suatu fraksi protein bioaktif dari *Lumbricus rubellus*, yang memiliki aktivitas antitrombotik, trombolitik, dan antiagregasi platelet, menawarkan strategi alternatif yang menarik. Laporan kasus di Indonesia oleh Pinzon *et al.* (2025) yang dimuat dalam *Medicinus* edisi ini memperlihatkan resolusi trombus tanpa perburukan perdarahan. Meskipun bukti tergolong masih dini, pendekatan ini menandai potensi biomedis lokal yang dapat bersaing dengan agen farmakoterapi global. Laporan ini menggambarkan seorang pria berusia 68 tahun dengan riwayat hipertensi dan diabetes melitus tipe 2 terkontrol, yang mengalami stroke hemoragik dengan perdarahan intrakranial di basal ganglia. Pada hari keenam perawatan, pasien mengalami tanda klinis trombotik vena dalam (*deep vein thrombosis*/DVT) yang terkonfirmasi melalui ultrasonografi dupleks. Tantangan muncul karena terapi standar berupa antikoagulan berisiko memperburuk perdarahan otak. Setelah dilakukan pemantauan dengan pencitraan yang menunjukkan hematoma yang stabil, pasien diberikan kombinasi LMWH dosis rendah dan DLBS1033. Selama terapi, tidak ditemukan perburukan neurologis atau perdarahan ulang, sementara gejala DVT berangsur membaik dan *follow-up* ultrasonografi memperlihatkan resolusi trombus. CT scan lanjutan menunjukkan perdarahan otak sudah terserap sempurna. Diskusi artikel menekankan bahwa DLBS1033 bekerja dengan memecah fibrin dan menghambat agregasi platelet, sehingga berpotensi sebagai agen tambahan atau alternatif untuk tata laksana DVT pada pasien stroke hemoragik. Laporan ini menyimpulkan bahwa DLBS1033 dapat menjadi opsi yang efektif dengan profil keamanan yang baik, meskipun diperlukan riset lebih lanjut untuk memastikan perannya dalam praktik klinis.

Etika dan Filosofi: Risiko, Waktu, dan Ketidakpastian

Keputusan terapeutik pada stroke hemoragik dengan DVT adalah pertarungan etis yang berlandaskan pada dimensi waktu. Hari-hari pertama adalah fase rentan dengan risiko tinggi perdarahan ulang, sedangkan minggu berikutnya adalah fase subakut dengan peningkatan risiko trombotik. Oleh karena itu, strategi yang diterapkan harus adaptif dengan menyesuaikan fase biologis pasien. Dari perspektif bioetika, keputusan ini melibatkan keseimbangan prinsip *autonomy*, *beneficence*, *nonmaleficence*, dan *justice* (Tjandrawinata, 2024). Ketidakpastian ini juga menegaskan bahwa kedokteran bukan ilmu pasti absolut, melainkan seni navigasi risiko dengan menggabungkan data, intuisi klinis, dan sensitivitas moral.

Perspektif Sistem Kesehatan: Kebijakan, Akses, dan Keadilan

Masalah DVT pascastroke hemoragik juga merefleksikan ketidakmerataan sistem kesehatan. *Intermittent pneumatic compression* (IPC) tidak selalu tersedia di rumah sakit kecil, CT scan serial yang direkomendasikan pada pedoman tidak selalu mudah diakses, dan *direct oral anticoagulant* (DOAC) tergolong mahal serta sering tidak ditanggung oleh asuransi

publik (Prabhakaran *et al.*, 2015). Dalam konteks negara berpendapatan menengah, hal ini menimbulkan kesenjangan keadilan kesehatan. Dari perspektif *health technology assessment* (HTA), diperlukan evaluasi *cost-effectiveness* dari intervensi seperti IPC, LMWH, atau DOAC untuk menentukan prioritas kebijakan. Sistem asuransi nasional, seperti Jaminan Kesehatan Nasional (JKN) di Indonesia, perlu memikirkan model pembiayaan yang memastikan akses luas ke intervensi yang terbukti efektif.

Pengelolaan DVT pada stroke hemoragik tidak mungkin berhasil bila dilakukan oleh satu spesialis saja. Kolaborasi antara spesialis neurologi, spesialis hematologi, ahli bedah vaskular, spesialis perawatan intensif, spesialis radiologi, hingga fisioterapis sangat diperlukan. *Integrated care pathway* yang melibatkan pencitraan serial, pemantauan laboratorium, mobilisasi dini, dan pengelolaan komorbiditas adalah suatu gambaran model ideal.

Dimensi Inovasi: Dari Protein Alami hingga Kecerdasan Buatan

Masa depan penatalaksanaan DVT pada stroke hemoragik akan ditentukan oleh inovasi. Agen biologis alami seperti DLBS1033 memberi alternatif nonkonvensional. Sementara itu, kecerdasan buatan dapat dimanfaatkan untuk membangun algoritma prediksi risiko individual, sehingga dapat membantu dokter menentukan pasien mana yang relatif berisiko rendah jika menerima antikoagulan dini, serta siapa yang lebih cocok dengan strategi mekanis (Liu *et al.*, 2014). Di sisi lain, *biomarker* baru, baik laboratorium maupun radiologi, dapat memberikan dasar objektif untuk menilai stabilitas hematoma dan risiko trombotik.

Kesimpulan

Pengelolaan DVT pada pasien stroke hemoragik merupakan cerminan kompleksitas kedokteran modern yang beroperasi di bawah bayang-bayang ketidakpastian. Paradoks terapeutik antara trombus dan hematoma menuntut keputusan yang menyeimbangkan ilmu, seni, dan etika. Strategi mekanis, farmakologis, dan alternatif biologis yang baru memiliki tempat masing-masing, namun harus selalu dipandu prinsip kehati-hatian dan sensitivitas konteks.

Lebih dari sekadar isu klinis, DVT pascastroke hemoragik adalah masalah kesehatan masyarakat yang menuntut respons multidisipliner, kebijakan kesehatan yang adil, serta keberanian dalam mengadopsi inovasi. Pada akhirnya, pengelolaan komplikasi ini adalah praktik menjaga keseimbangan dalam ketidakpastian, memanusiakan pasien, serta memastikan keadilan dalam akses layanan kesehatan.

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Association Between Neutrophil-to-Lymphocyte Ratio (NLR) and Dengue Severity in Patients Treated at Bethesda Hospital, Yogyakarta

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Abstract

Background: Dengue fever, a mosquito borne viral infection, remains a major public health concern in Indonesia, with the challenges in early identification of severe cases. The neutrophil-to-lymphocyte ratio (NLR) has emerged as a potential biomarker for assessing the disease severity.

Objective: This study aimed to investigate the association between NLR and dengue severity in patients treated at Bethesda Hospital, Yogyakarta.

Methods: A cross-sectional, quantitative study was conducted using medical record data from dengue patients admitted between 2022 to 2024. The NLR values were calculated from complete blood count results and disease severity was classified according to WHO guidelines. Statistical analysis was performed using the chi-square test and Fisher's exact test.

Results: Among the 68 patient samples, a significant association was found between NLR and dengue severity ($p < 0.001$). Patients with lower NLR values were more likely to develop dengue hemorrhagic fever (DHF) compared to those with higher NLR values.

Conclusion: The NLR plays a role in determining the severity of dengue infection and may serve as a predictive biomarker. This examination can be a practical tool in the clinical management of dengue fever patients, particularly for early detection and optimizing therapeutic decision-making.

Keywords: dengue fever, neutrophil-to-lymphocyte ratio, dengue hemorrhagic fever, biomarker, disease severity, Bethesda Hospital, Indonesia

Abstrak

Latar belakang: Demam berdarah dengue (DBD) merupakan penyakit infeksi virus yang ditularkan melalui gigitan nyamuk dan masih menjadi salah satu permasalahan kesehatan masyarakat di Indonesia. Salah satu tantangan dalam penanganan penyakit ini adalah identifikasi dini pada kasus yang parah. Rasio neutrofil terhadap limfosit (*neutrophil-to-lymphocyte ratio*/NLR) menjadi *biomarker* potensial untuk menilai tingkat keparahan penyakit demam berdarah.

Tujuan: Studi ini bertujuan untuk mengetahui hubungan antara NLR dan tingkat keparahan DBD pada pasien demam berdarah di Rumah Sakit Bethesda, Yogyakarta.

Metode: Studi ini merupakan studi *cross-sectional* dengan pendekatan kuantitatif. Data yang digunakan dalam studi ini diambil dari rekam medis pasien DBD yang dirawat antara tahun 2022 hingga 2024 di Rumah Sakit Bethesda, Yogyakarta. Nilai NLR didapatkan dari hasil hitung darah lengkap, sedangkan tingkat keparahan penyakit diklasifikasikan berdasarkan pedoman WHO. Selanjutnya, analisis statistik dilakukan menggunakan uji *chi-square* dan uji Fisher's *exact*.

Hasil: Dari 68 sampel pasien yang dianalisis, ditemukan adanya hubungan yang signifikan antara nilai NLR dan tingkat keparahan DBD ($p < 0,001$). Pasien dengan nilai NLR yang lebih rendah memiliki risiko lebih tinggi untuk mengalami demam berdarah dengue berat (DHF) dibandingkan dengan pasien dengan nilai NLR yang lebih tinggi.

Kesimpulan: NLR berperan dalam menentukan tingkat keparahan infeksi dengue dan dapat digunakan sebagai *biomarker* prediktif. Pemeriksaan ini dapat digunakan sebagai salah satu parameter yang praktis dalam penanganan pasien DBD, khususnya untuk deteksi dini dan mengoptimalkan terapi pasien demam berdarah.

Kata kunci: demam berdarah, rasio neutrofil terhadap limfosit, demam berdarah dengue berat, *biomarker*, tingkat keparahan, Rumah Sakit Bethesda, Indonesia

Introduction

Dengue fever is a viral infectious disease that remains a global health concern, particularly in tropical and subtropical regions such as Indonesia. Transmission of the dengue virus (DENV) occurs through bites from *Aedes aegypti* and *Aedes albopictus* mosquitoes. The clinical presentation of dengue varies widely, ranging from high fever and muscle pain to bleeding tendencies, which may progress to more severe forms such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). According to the World Health Organization (WHO), approximately 3.4 million dengue cases were reported worldwide, with over 3,000 deaths.¹ In Indonesia, the number of dengue cases continues to increase, with Yogyakarta being one of the most affected regions.²

Dengue fever presents a broad spectrum of clinical manifestations and often progresses in an unpredictable manner. According to WHO classification, dengue is categorized based on severity into dengue fever (DF) and dengue hemorrhagic fever (DHF), further subdivided according to clinical symptoms and laboratory findings.¹

One of the main challenges in dengue management is accurately assessing the disease severity.³ Laboratory tests such as NS1 ELISA and serology (IgM/IgG) are considered the gold standard for diagnosis. However, these tests are not always available in remote areas and are relatively expensive.⁴ Therefore, more accessible and cost-effective methods are needed to predict the disease severity. A promising marker is the neutrophil-to-lymphocyte ratio (NLR), which represents the balance between neutrophils and lymphocytes in peripheral blood and reflects the body's immune response to infection.⁵ In healthy adults, the normal NLR range is between 1.0 and 3.5; values below 1 indicate a higher lymphocyte count, whereas values above 3.5 suggest a significant increase in neutrophils.⁶

This study examines the association between NLR and dengue severity at Bethesda Hospital, Yogyakarta. Understanding the role of NLR in disease progression supports early diagnosis and guides more appropriate treatment strategies, ultimately reducing complications and improving patient outcomes.

Methods

This study employed a cross-sectional and quantitative approach to analyze the association between the NLR and the dengue fever severity. The cross-sectional approach enabled data collection at a single point in time—specifically when patients were diagnosed with dengue—using secondary data from medical records at Bethesda Hospital, Yogyakarta. All relevant data, including NLR values and dengue severity classification, were collected simultaneously during the defined research period.

Secondary data were obtained from the medical records of dengue patients treated at Bethesda Hospital, Yogyakarta between 2022 to 2024. This study received official approval from the Ethics Commission for Health Research (Komisi Etik Penelitian Kesehatan/KEPK) of Bethesda Hospital, Yogyakarta with permit number 08441/KC.0267/2024 and ethical

clearance number 58/KEPK-RSB/XII/24. Data collection was conducted from December 2024 to January 2025. A total of 400 samples were initially retrieved, and after applying inclusion and exclusion criteria, 68 samples were selected for final analysis. These records provided the necessary information on neutrophil-lymphocyte ratio (NLR) values and dengue severity, which served as the core variables of this study. The sample size was estimated using the Lameshow estimation formula to ensure adequate statistical power. The collected data were then grouped according to research variables.

The independent variable was the neutrophil-to-lymphocyte ratio, categorized into low, normal, and high. The dependent variable was dengue severity and classified into two groups: dengue fever (DF) and dengue hemorrhagic fever (DHF), with equal sample sizes of 34 in each category. Age and gender were considered as potential confounding variables.

All data were analyzed using SPSS software. Univariate analysis described patient characteristics, while bivariate analysis with the chi-square test or Fisher’s exact test evaluated the association between NLR and dengue severity. Ethical principles—respect for persons, beneficence, nonmaleficence, and justice—were strictly observed throughout the study.

Results

a. Baseline Data Characteristic

Table 1. Baseline data characteristic (n= 68)

Characteristic	n	%
Gender		
- Male	38	55.9%
- Female	30	44.1%
Age (years)		
- 18–25 years	33	48.5%
- 26–35 years	20	29.4%
- 36–45 years	15	22.1%
NLR		
- Low	2	2.9%
- Normal	34	50%
- High	32	47.1%

Among the 68 analyzed samples, the majority patients were male (55.9%). Nearly half of the patients were late adolescents (18–25 years), representing for 48.5% of the total. In terms of NLR distribution, 2.9% of patients had low values, 50% fell within the normal range, and 47.1% presented with high levels.

b. Relationship of Neutrophil to Lymphocyte Index with Dengue Severity

Table 2. The role of gender in dengue severity

Variables	DF (%)	DHF (%)	p-value
Gender			0.625
Male	20 (29.4%)	18 (26.5%)	
Female	14 (20.6%)	16 (23.5%)	

Based on **Table 2**, dengue patients were predominantly male (n= 38), with 20 patients (29.4%) were diagnosed with dengue fever (DF). Among female patients (n= 30), 16 (23.5%) patients were diagnosed with DF. The Pearson chi-square test yielded a *p*-value of 0.625. Since the *p*-value is greater than 0.05, there is no statistically significant association between gender and dengue severity. These findings suggest that gender does not influence the severity of dengue in this sample.

Table 3. The role of NLR in dengue severity

Variables	DF (%)	DHF (%)	p-value
NLR			
- Low/Normal	10 (29.4%)	25 (73.5%)	<0.001
- High	24 (70.6%)	9 (26.5%)	

The Fisher's exact test produced a *p*-value of <0.001, well below the significance threshold (*p*<0.05), indicating a statistically significant association between NLR and dengue severity. Patients with low or normal NLR values were more likely to develop dengue hemorrhagic fever (DHF), while those with high NLR values were more frequently diagnosed with dengue fever (DF). These findings support the initial hypothesis that a decreased NLR may be associated with increased disease severity in dengue infection.

Discussion

This study investigated the association between NLR and the dengue infection severity at Bethesda Hospital, Yogyakarta. Among the 68 analyzed samples, the gender distribution was dominated by male patients (n=38; 55.9%) compared to female patients (n=30; 44.1%). Statistical analysis showed a *p*-value of 0.625 (*p*>0.05), indicating no significant association between gender and dengue severity. These findings suggest that gender does not have a meaningful impact on the clinical progression of dengue in this study. This result is in contrast with a previous study by Kharisma *et al.* (2021) with a larger sample size (n=100), and reported the male patients had a 31.8% higher to develop dengue hemorrhagic fever (DHF) than female patients.⁷ The difference may be influenced by hormonal factors, especially testosterone, which is known to suppress immune function through several mechanisms involving both innate and adaptive immunity. This include reducing the production of proinflammatory cytokines (TNF-α, IL-1β, IL-6), increasing anti-inflammatory IL-10, inhibiting T-cell proliferation, and lowering monocyte counts and CD4+/CD8+ ratios.⁸ These effects may weaken the body's immune and inflammatory responses, potentially contributing to more severe outcomes in male patients.⁸

In this study, based on age categories, the highest number of infections was observed in the late adolescent group (18–25 years; n=33), followed by the early adult group (26–35 years; n=20) and the late adult group (36–45 years; n=15). These findings are consistent with the previous research by Avidsyahh *et al.*(2024), suggesting that younger individuals are more

likely to develop dengue due to activity patterns that increase exposure to *Aedes aegypti* bites.⁹ People in this age group tend to be more active outdoors during peak mosquito biting hours, which increase their risk of infection.⁹ These results also align with finding from a research conducted by Buonacera *et al.* (2022), which reported that dengue fever commonly affects individuals in the productive age group and does not show significant differences between genders. This trend is influenced by environmental exposure and daily activity level, as people in the productive age group are typically more active in the morning and evening, coinciding with the active periods of the *Aedes aegypti* mosquito.¹⁰

Bivariate analysis revealed a significant association between NLR category and dengue severity, as measured using the Fisher's exact test ($p < 0.001$). This result supports the initial hypothesis that a lower NLR may contribute to increased severity in dengue fever. The dengue virus induces lymphocyte destruction as part of the adaptive immune response, leading to a decrease in circulating lymphocytes and the emergence of atypical lymphocytes, particularly during the critical phase of infection.¹¹ In parallel, the dengue virus also triggers an acute inflammatory response that increases neutrophils levels. This imbalance, as indicated by abnormal NLR values, reflects a disruption in the regulating the body's immune response.¹² In such condition, the body may struggle to control inflammation effectively, increasing the risk of complications and worsening the clinical prognosis. The study also found that patients with low NLR values had a higher risk of developing dengue hemorrhagic fever (DHF) compared with high NLR values, as shown by the sample distribution and p -value < 0.001 . These findings suggests that low NLR values in dengue patients may reflect underlying pathological mechanisms such as T-lymphocytes or cytokines overactivation, increased plasma leakage, and imbalance between pro- and anti-inflammatory cytokines that all of which contribute to disease severity. An imbalance between neutrophils and lymphocytes may indicate an inadequate immune response, leading to a higher risk of severe outcomes. Therefore, NLR can be considered a useful marker for predicting dengue severity and may serve as a practical diagnostic tool to support early detection and timely clinical intervention.¹³

In addition, these findings have important clinical implications, for the management of dengue patients. NLR may serve as a valuable marker for identifying individuals at risk of severe disease and guiding early clinical attention. This result is consistent with the recommendations of a previous study by Buonacera *et al.* (2022), which emphasized the role of NLR in the management of dengue patients.¹⁰ That study also highlighted the broader importance of hematological biomarkers in predicting clinical outcomes in dengue, a point reaffirmed by Ishaque *et al.* (2022), who noted that NLR values can be used to estimate disease severity and monitor immune response imbalance.⁵ This study used secondary data obtained from patient medical records, without direct clinical examination. In several cases, the medical records were incomplete, with laboratory results documented only once during patient care and not recorded serially. As a result, the assessment of the association between NLR and dengue severity was based on a single time point, which does not capture the dynamic progression of the disease.

Due to sample limitations, this study did not investigate the association between confounding variables—such as age and gender—and the independent variable of NLR. Therefore, these confounding variables in the study were not controlled in the analysis, which may affect the interpretation of the association of NLR with dengue severity.

Conclusion

The findings of this study demonstrate a significant association between the NLR and dengue severity in patients treated at Bethesda Hospital, Yogyakarta. These results suggest that NLR may serve as a useful biomarker for predicting disease progression and guiding clinical management. For future research, a longitudinal study design is recommended to better capture the dynamic changes in NLR throughout the course of dengue infection. This approach would allow for more accurate analysis of severity risk using statistical measures such as odds ratio (OR) and rate ratio (RR). Additionally, the timing of fever onset should be considered, as it may influence laboratory results and disease trajectory. It is also

recommended to include a larger sample size and a broader age range in future studies to enable a more comprehensive and statistically robust analysis.

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Conflict of Interest and Funding Resources

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The Benefit of DLBS1033 for Deep Vein Thrombosis in A Hemorrhagic Stroke Patient: A Case Report

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Abstract

Background: Deep vein thrombosis (DVT) is a significant complication in patients with hemorrhagic stroke, primarily due to prolonged immobility. Although anticoagulants are routinely used for DVT prophylaxis in stroke patients, its application in hemorrhagic stroke remains controversial due to the increased risk of intracranial bleeding. This resulting in a challenging balance between preventing DVT and avoiding further hemorrhage. DLBS1033, a bioactive protein fraction from the earthworm *Lumbricus rubellus*, demonstrated antithrombotic, thrombolytic, and antiplatelet aggregation activities, offering a potential alternative therapeutic approach in such cases.

Case report: A 68-year-old male with history of chronic hypertension and well-controlled type 2 diabetes mellitus presented to the emergency department with drowsiness and left-sided hemiparesis, subsequently diagnosed as intracerebral hemorrhage. On the sixth day of hospitalization, the patient developed DVT. DLBS1033 was administered as part of the management strategy.

Conclusions: This case report demonstrates the effective and safe use of DLBS1033 in managing DVT for patient with hemorrhagic stroke. DLBS1033 is considered a potential promising agent for treating thrombus-related diseases.

Keywords: DVT, deep vein thrombosis, hemorrhagic stroke, anticoagulant, DLBS1033, *Lumbricus rubellus*

Abstrak

Latar belakang: Trombosis vena dalam (TVD) atau *deep vein thrombosis* (DVT) merupakan komplikasi yang signifikan pada pasien dengan strok hemoragik, terutama karena imobilitas berkepanjangan. Meskipun antikoagulan secara rutin digunakan untuk profilaksis DVT pada pasien strok, penggunaannya dalam strok hemoragik masih kontroversial karena peningkatan risiko perdarahan intrakranial. Hal ini menyebabkan tantangan kesetimbangan antara mencegah DVT dan menghindari perdarahan lanjutan. DLBS1033, fraksi bioaktif protein dari cacing tanah *Lumbricus rubellus* menunjukkan aktivitas antitrombotik, trombolitik, dan antiagregasi platelet, menawarkan alternatif pendekatan terapeutik potensial untuk kasus tersebut.

Laporan kasus: Seorang laki-laki berusia 68 tahun dengan riwayat hipertensi kronis dan diabetes melitus tipe 2 yang terkontrol dibawa ke unit gawat darurat dengan kondisi rasa kantuk dan hemiparesis sisi kiri, selanjutnya didiagnosis dengan perdarahan intrakranial. Pada hari ke-6 perawatan di rumah sakit, pasien mengalami DVT. DLBS1033 diberikan sebagai bagian dari strategi tata laksana.

Kesimpulan: Laporan kasus ini menunjukkan penggunaan DLBS1033 yang efektif dan aman dalam menangani DVT pada pasien strok hemoragik. DLBS1033 dianggap sebagai agen potensial yang menjanjikan untuk mengobati penyakit terkait trombus.

Kata kunci: DVT, trombosis vena dalam, strok hemoragik, antikoagulan, DLBS1033, *Lumbricus rubellus*

Introduction

Deep vein thrombosis (DVT) is a common and potentially life-threatening complication in patients hospitalized with reduced mobility, including those patients with stroke.¹ Following an intracerebral hemorrhage, patients often experience motor paralysis, which leads to venous stasis in the dependent limbs.² In addition, acute brain injury induces endothelial dysfunction, releases proinflammatory cytokines, and alters coagulation pathways, all of which contribute to a prothrombotic state, further increasing the risk of clot formation.³

The incidence of DVT in patients with hemorrhagic stroke has been reported to be higher than in those with ischemic stroke.⁴ The onset of DVT after stroke can occur very early, with reports indicating that thrombi may begin to form as early as the second day following the event. The risk is highest within the first week, peaking between day 3 and 7, although DVT formation may continue well into the subacute and recovery phases. Several studies have demonstrated that the mean or median time to symptomatic venous thromboembolism diagnosis is approximately 5 to 20 days after stroke onset.⁵ Importantly, if left untreated, proximal DVT carries a significant clinical burden, with an estimated 15% risk of death, largely due to pulmonary embolism as the most feared complication.^{5,6} While DVT is frequently discussed in the context of ischemic stroke, its occurrence in hemorrhagic stroke presents unique challenges for clinicians due to the delicate balance between the risks of thrombosis and rebleeding.^{1,4}

Preventing DVT in patients with hemorrhagic stroke remains challenging, as anticoagulants—the standard therapy for DVT—can increase the risk of further bleeding.⁴ This case report aims to highlight the use of DLBS 1033 in the management of a patient who developed a deep vein thrombosis following a hemorrhagic stroke, and to discuss the complexities and clinical considerations in managing such cases.

Case Report

A 68 year-old male with a medical history of chronic hypertension and well-controlled type 2 diabetes mellitus was brought to the emergency department following the sudden onset of left-sided weakness and altered consciousness. On examination, the patient was hypertensive (BP 220/120 mmHg), drowsy, and exhibited left hemiparesis, with a Glasgow Coma Scale (GCS) score of 11.

An urgent non-contrast computed tomography (CT) scan of the brain was performed and revealed an intracerebral hemorrhage (ICH) located in the right basal ganglia region. The estimated volume of the hemorrhage was approximately 25 ml, accompanied by surrounding edema. Notably, there was no evidence of intraventricular extension of the bleed, nor was any midline shift observed on the imaging (**Figure 1**). Laboratory investigations showed that the patient's complete blood count was within normal limits. Additionally, renal and liver function tests, as well as blood glucose levels (which were maintained within the normal range with medication), were all unremarkable. Electrolyte level was also found to be normal. Based on these findings, the patient was admitted to the stroke intensive care unit for continuous monitoring and appropriate medical management.

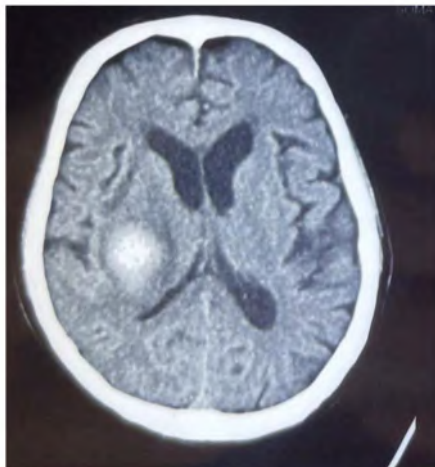


Figure 1. Initial brain CT scan

The initial management focused on controlling blood pressure, elevating the head of the bed, and providing supportive care without surgical intervention. The patient remained clinically stable with no signs of herniation. In the following days, the patient was largely immobile due to persistent neurological deficits and generalized weakness. Physical therapy and passive limb exercises were initiated as early as possible and tolerated; however, progress was limited due to fluctuating consciousness and overall clinical condition.

On day 6 of hospitalization, the patient developed swelling and mild erythema of the right lower extremity, which was tender to palpation. There was no prior history of venous thromboembolism or inherited thrombophilia. Duplex ultrasonography of the affected limb confirmed the presence of an acute DVT involving the left femoral and popliteal veins (**Figure 2**). The D-Dimer level was 968 ng/ml (normal value <500 ng/ml).



Figure 2. The diagnosis of DVT from doppler ultrasound

In this patient, acute left limb DVT was diagnosed based on duplex ultrasonography findings and elevated D-Dimer level. The patient had significant risk factors: (1) prolonged immobility leading to venous stasis; (2) inflammatory and prothrombotic state induced by acute brain injury; and (3) comorbid conditions such as hypertension and diabetes mellitus.

Unlike ischemic stroke, the use of pharmacological prophylaxis in hemorrhagic stroke remains controversial due to the potential risk of exacerbating intracerebral bleeding. Given the confirmed DVT and the elapsed time from intracerebral hemorrhage (ICH) onset (on day 6), a multidisciplinary team discussion was held, involving neurology, hematology, and

critical care specialists. Repeat neuroimaging confirmed stability of the hemorrhage with no evidence of expansion. Based on these findings, we initiated low-dose low molecular weight heparin (LMWH) for three days under close neurological monitoring for any neurological deterioration and serial imaging to detect any sign of rebleeding. Concurrently, DLBS1033 was administered three times daily for ten days.

The patient tolerated anticoagulation well, without any evidence of neurological deterioration or rebleeding. Swelling and tenderness of the affected limb gradually improved. Over the next two weeks, the patient's neurological status stabilized, allowing for a gradual intensification rehabilitation efforts. Follow-up duplex ultrasonography demonstrated resolution of the thrombus. DLBS1033 was discontinued after two weeks. A repeat CT scan was performed at the end of weeks 3, which showed complete resolution of the intracerebral hemorrhage (**Figure 3**).



Figure 3. Follow up CT scan

Discussion

We reported a safe and promising therapeutic approach using DLBS1033 for the treatment of DVT in patients who experienced a hemorrhagic stroke. DLBS1033 is a specific protein extract derived from the earthworm species *Lumbricus rubellus*, which has been demonstrated both antithrombotic and thrombolytic properties. This natural protein extract primarily acts by degrading fibrin clots, and inhibiting platelets aggregation, making it a potentially effective agent for managing thrombus-related disease.⁷ According to previous clinical studies, DLBS1033 has shown efficacy in treating various embolic and vascular diseases.⁸ DLBS1033 mechanism of action involves breaking down the complex structure of blood clots, which are primarily composed of fibrin and platelets. The extract can penetrate clots and facilitate fibrin degradation, ultimately leading to clot lysis.⁷ Due to this dual mechanism, DLBS1033 is regarded as a potentially valuable therapeutic agent for managing thromboembolic disease. It has also demonstrated potential as an adjunctive therapy in management of patients with conditions such as pulmonary embolism (PE) and peripheral arterial disease, further supporting its role in vascular health management.^{7,8}

The development of DVT following stroke follows a well-documented time course. Studies have shown that thrombi may form as early as the second day poststroke, with peak incidence between day 3 and 7. Symptomatic venous thromboembolism emerges between 5 and 20 days after stroke onset, as demonstrated in this case, where DVT was identified on day 6.⁵ DVT should be suspected in stroke patients presenting with unilateral limb swelling, pain, erythema, and tenderness, particularly in the context of recent immobility. However, clinical signs alone are not sufficiently sensitive

or specific. Duplex ultrasonography remains the gold standard for diagnosis, as it is noninvasive, widely available, and highly sensitive.⁹ Management of DVT in the context of hemorrhagic stroke presents a major therapeutic dilemma. While therapeutic anticoagulation is the cornerstone of DVT treatment, it carries a risk of rebleeding in patients with recent ICH.⁵

Managing DVT following ICH requires careful consideration of two key factors. The first is the timing of anticoagulation, which is typically postponed for 7 to 14 days following the onset of ICH. This delay allows clinicians to evaluate the stability and volume of the hemorrhage and to ensure neurological stabilization before initiating therapy that may elevate the risk of rebleeding. The second consideration involves the selection of anticoagulant agents. Both low-molecular-weight heparin (LMWH) and unfractionated heparin are potential viable options; however the choice should always be individualized based on the patient's clinical status and risk profile. In this context, our study highlights the potential benefit of DLBS1033 as a promising therapeutic agent, offering an alternative strategy for managing thrombus formation in patients where anticoagulation carries substantial risk.

In this study, the patient tolerated DLBS1033 well, with gradual improvement in limb symptoms, and no evidence of neurological deterioration or hematoma expansion. These findings suggest that DLBS1033 may offer a safer alternative or adjunctive therapy in scenarios where anticoagulation carries a high risk. Over the subsequent two weeks, the patient's neurological status stabilized and rehabilitation efforts were progressively intensified. Follow-up duplex ultrasonography confirmed resolution of the thrombus. The patient was discharged from hospital with mild residual disability.

Multiple studies have highlighted the elevated risk of thromboembolic events in patients with hemorrhagic stroke, particularly during the subacute phase when mobility remains limited.^{7,10} Anticoagulation, the cornerstone of DVT treatment, can significantly increase the risk of hematoma expansion and secondary intracranial bleeding. The decision to initiate anticoagulation must be individualized and guided by a careful risk-benefit assessment. Current guidelines recommend delaying anticoagulant for at least 7 to 14 days, depending on the size and stability of the hemorrhage, as well as the patient's neurological status. In the meantime, mechanical prophylaxis, such as early mobilization and intermittent pneumatic compression devices, is commonly employed as a safer preventive strategy.¹⁰

Conclusion

DVT is a serious complication in patients with hemorrhagic stroke, primarily due to the complex challenge of balancing thrombotic and hemorrhagic risks. This case report highlights a safe therapeutic approach using DLBS1033 in the management of DVT following intracerebral hemorrhage. DLBS1033 may represent an innovative therapeutic adjunct or alternative pathway in this setting; however, further research is warranted to define its roles in clinical practice. Until then, a multidisciplinary strategy—including careful patients selection, timely neuroimaging, mechanical prophylaxis, and individualized pharmacologic approach—remains the cornerstone of safe and effective DVT management in patients with hemorrhagic stroke.

Disclosure

Verbal informed consent was obtained from the patient. No patient identity can be revealed.

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A Patient with Non-Hodgkin's Lymphoma of The Spinal Region with Tuberculosis Spondylitis Infection: A Case Report

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Abstract

Primary non-Hodgkin's lymphoma (NHL) of spinal origin is very rare, accounting for only 0.1% of all NHL, with spinal cord compression is the first symptom. Tuberculosis (TB) spondylitis is a chronic granulomatous inflammatory disease of the spine caused by *Mycobacterium tuberculosis*. Some patients will experience neurological deficits. If the *M. tuberculosis* bacterial infection affects the vertebral body, the resulting damage causes spinal instability and disruption of the surrounding structures. Patients can experience paraparesis or tetraparesis due to compression of the spinal cord. This disease has symptoms such as back pain, kyphosis, and constitutional syndrome. A case of a 75-year-old male patient with non-Hodgkin's lymphoma diffuse large cell region spine stage IV ECOG 4, tuberculosis spondylitis on antituberculosis drugs special regimen intensive phase.

Keywords: non-Hodgkin's lymphoma, spine region, TB spondylitis

Abstrak

Non-Hodgkin's *lymphoma* (NHL) primer yang berasal dari tulang belakang adalah sangat jarang, hanya 0,1% dari seluruh NHL, dan kompresi medula spinalis merupakan gejala awalnya. Spondilitis tuberkulosis (TB) adalah penyakit inflamasi granulomatosa kronis pada tulang belakang yang disebabkan oleh *Mycobacterium tuberculosis*. Beberapa pasien akan mengalami defisit neurologis. Jika infeksi bakteri *M. tuberculosis* memengaruhi korpus vertebra, kerusakan yang dihasilkan menyebabkan instabilitas tulang belakang dan disrupti pada struktur sekitarnya. Pasien dapat mengalami paraparesis atau tetraparesis akibat kompresi medula spinalis. Penyakit ini memiliki gejala-gejala seperti nyeri punggung, kifosis, dan sindrom konstitusional. Dilaporkan suatu kasus pada pasien laki-laki berusia 75 tahun dengan NHL sel besar difus regio tulang belakang stadium IV ECOG 4, spondilitis tuberkulosis dalam terapi obat antituberkulosis regimen khusus fase intensif.

Kata kunci: non-Hodgkin's *lymphoma*, area spinal, spondilitis tuberkulosis

Introduction

Malignancy is one of the leading causes of death in the world. It is estimated that there are 14 million new cases of malignancy and 8.2 million deaths due to malignancy in the world. One of the most common malignancies is lymphoma. Lymphoma is a group of diseases caused by the accumulation of malignant lymphocyte cells in the lymph nodes and other lymphoid tissues. In general, lymphoma is divided into two groups: non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). About 85% of all lymphomas are non-Hodgkin's lymphoma (NHL).¹

NHL is defined as a group of primary malignancies of lymphocytes and extranodal lymphoid tissues, which can originate from B lymphocytes, T lymphocytes, and NK (natural killer) cells originating from the lymph node systems; which is very heterogeneous, both in histological type, symptoms, clinical course, response to treatment, and prognosis.⁹ Some of these lymphomas develop very slowly (in years), while others spread rapidly (in months). Compared with Hodgkin's lymphoma, non-Hodgkin's lymphoma has a greater predilection for spreading to extranodal locations.¹

The incidence of NHL increased in frequency by approximately 4% per year in the United States and 2–8% per year globally between 1950 and the late 1990s. In 2014, there were 70,800 new cases of NHL in the United States and nearly 360,000 new cases worldwide. NHL incidence has continued to increase in particular and now ranks seventh among all cancers worldwide. NHL is more common in elderly and is more frequently in males.^{1,2}

In Indonesia, NHL is ranked as the sixth most common cancer. According to the National Coordinating Board of Hematology Oncology Internal Medicine of Indonesia, the incidence of lymphoma is higher than leukemia and is ranked the third fastest growing cancer after melanoma and lung cancer. NHL with extranodal tissue involvement, particularly bone, accounts for approximately 5% of extranodal cases and 7% of all bone tumors. The bones most frequently affected include the ilium, scapula, vertebrae, femur, and tibia. Based on histopathology, the most often found is diffuse large B cell lymphoma. In the literature, lymphoma localized in the thoracolumbar region has been reported with difficulty in differential diagnosis with nonspecific infections, such as tuberculosis.³ Based on other literature, primary skeletal lymphoma is rare, only 1% of NHL originates from the bone. In practice, primary NHL originating from the spine is very rare, only 0.1% of all NHL, and spinal cord compression is the first symptom. In TB-endemic countries, tuberculosis is the first diagnosis for patients with spinal cord compression.^{2,4}

Tuberculosis (TB) spondylitis is a chronic granulomatous inflammatory disease of the spine caused by *Mycobacterium tuberculosis*. As many as 50% of patients with TB spondylitis have lesions in the spine and 10–45% of them experience neurological deficits. Spine is the most common location of bone tuberculosis infection, which is around 50% of cases of osteoarticular tuberculosis. If the *M. tuberculosis* bacterial infection affects the vertebral corpus, the damage that occurs causes spinal instability and disruption of the surrounding structures. Patients can be paralyzed due to compression of the spinal cord.⁵

Tuberculosis spondylitis is a common form of extrapulmonary disease. This disease is popularly known as Pott disease which is one of the common causes of spinal infection in developing countries and endemic areas. This disease has symptoms such as back pain, kyphosis, constitutional syndrome, and fever. 50% of patients show neurological complications due to spinal cord compression or direct invasion, developing myeloradiculopathy with paraparesis or tetraparesis in 10–27%.⁶ Approximately 10% of patients with extrapulmonary tuberculosis have bone involvement. Spine is the most common skeletal site affected, followed by the hip and knee. Spinal tuberculosis accounts for almost 50% of cases of bone tuberculosis.^{5,6}

The etiology of non-Hodgkin's lymphoma is not yet known for certain. However, there are several risk factors for NHL, including age, gender, genetics, exposure to chemicals, viral or bacterial infections, and autoimmune.⁶

Patients with primary and secondary immunodeficiency states are one of the predispositions to develop lymphoma. B-cell lymphoma is more common in Asia than in Western countries, while certain subtypes of B lymphoma such as follicular lymphoma are more common in Western countries.^{6,7}

Case Presentation

A 75-year-old male patient presented with complaints of weakness in both legs that had been experienced since 2 months ago, and had worsened over the past week. The patient experienced a sudden onset of weakness in both leg, which made him difficult to walk and only lay in bed. He denied pain and numbness in the leg but reported lower back pain that had persisted for two months. It was intermittent pain with duration around 15–20 minutes, moderate intensity, and non-radiating. He could not hold his urine and bowel movements and decreased appetite had been present for approximately one month prior to admission. He experienced fluctuating fever that persisted for 3 weeks and relieved by consuming paracetamol. A weight loss of approximately 10 kg was observed in the patient within one month.

In May 2022, the patient was diagnosed with non-Hodgkin's lymphoma in the spine and history of TB spondylitis. The history of medicinal used by the patient was a special regimen of antituberculosis consisting of ethambutol (1 x 100 mg), ofloxacin (2 x 400 mg), and rifampicin (1 x 600 mg) since May 6, 2022.

On physical examination, the patient was compos mentis with blood pressure of 120/60 mmHg, pulse rate of 100 beats per minute, respiratory rate of 20 times per minute, axillary temperature of 37°C, visual analog score of 3/10, and oxygen saturation 98% in room air. On June 14, 2022, laboratory examination revealed leukocytes $9.09 \times 10^3/\mu\text{L}$, neutrophils $7.05 \times 10^3/\mu\text{L}$, lymphocytes $1.1 \times 10^3/\mu\text{L}$, basophils $0.01 \times 10^3/\mu\text{L}$, monocytes $0.86 \times 10^3/\mu\text{L}$, eosinophils $0.07 \times 10^3/\mu\text{L}$, hematocrit 29.1%, MCV 86.1 fl, MCH 29.6 fl, hemoglobin 10 g/dl, and platelets $432 \times 10^3/\mu\text{L}$. Blood chemistry examination showed SGOT 71.4 U/l, SGPT 61.9 U/l, BUN 15.6 mg/dl, and creatinine 0.78 mg/dl. Blood culture showed no growth. Spinal TB PCR was positive, but molecular rapid test results with the conclusion of MTB were not detected.

Histopathological examination of spinal biopsy on May 6, 2022 concluded malignant round cell tumor, with histomorphology tends to be non-Hodgkin's lymphoma, diffuse, large cell. The results of the immunohistochemistry examination conducted on May 17, 2022, revealed CK (-)/CD 45 (+)/CD 3 (+)/CD 20 (+)/Ki 67 (+) 80–90%, with the conclusion that the immunohistochemistry staining pattern is more suitable for non-Hodgkin's lymphoma, diffuse, large cell originating from B cells (CD 20 positive).

On June 15, 2022, the radiological examinations, MRI spine with contrast, were performed, showed the impression pre- and paravertebral soft tissue right and left (dominant left) at the level of CV T8-L4 which pushed the abdominal aorta and pressed the inferior vena cava at that level, which extended to m. psoas major right and left, m. spinal thoracic right and m. rotatores thoracic right at the level of T11-L1, m. intercostal and subcostae at the level of T11 - left, neural foramina right and left at the level of T9-T10 and T10-T11. This results caused pressure on the spinal cord at that level and suspected of infiltrating the exiting nerve root T9 and T10 right and left, suggesting a malignant mass with abscess formation in it, possibly accompanied by a specific process.



Figure 1. MRI spine + contrast

Based on anamnesis, physical examination, and supporting investigations, it was concluded that the patient was diagnosed with observation of upper motor neuron (UMN) type paraparesis with suspected cause of compression myelopathy and transversemyelitis and tuberculosis, in the setting of tuberculosis spondylitis under a special intensive phase antituberculosis regimen. The patient was also diagnosed with diffuse non-Hodgkin's lymphoma large cell spine region stage IV ECOG 4. At that time, the patient consulted a neurologist and was treated with mecobalamin 500 mg every 12 hours intravenously, pramipexole 0.375 mg every 24 hours per oral and the patient was planned to undergo chemotherapy with the RCHOP regimen (rituximab 600 mg, cyclophosphamide 1000 mg, doxorubicin 70 mg, vincristine 2 mg, and prednisone 20 mg every 8 hours per oral from the first day 1 to 5). Treatment of TB spondylitis is also continued with ethambutol 100 mg, ofloxacin 400 mg every 12 hours orally, and rifampicin 600 mg.

Discussion

Non-Hodgkin's lymphoma is a group of primary lymphocyte malignancies originating from B lymphocytes, T lymphocytes, and natural killer (NK) cells. NHL is divided into two groups based on its prognosis, namely 'indolent' and 'aggressive'. Aggressive lymphomas include diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, precursor B-cell and T-cell lymphoblastic leukemia/lymphoma, adult T-cell leukemia/lymphoma, and certain other peripheral T-cell lymphomas.^{9,10}

Based on the history of a 75-year-old male patient, epidemiologically it is most common in individuals aged 65–75 years, with a mean age of 67 years, and occurs more frequently in men. NHL accounts for 85% of lymphoma cases, with the majority being diffuse large B-cell lymphoma. Primary tumors of the spine are most commonly located in the thorax spine, followed by the cervical spine, and less commonly in the lumbar spine. The predominance in the thoracic spine location is thought to be due to its plasticity, which allows for the development of large diseases, in addition to its superior length and more concentrated lymphatic drainage. Spinal lymphoma is predominantly found in males with a 1.6:1 male-to-female ratio. The exact etiology of NHL remains largely unknown.¹⁰

Based on the anamnesis and physical examination, the patient reported intermittent fever and weight loss. In the literature, non-Hodgkin's lymphoma is associated with "B symptoms," which include fever, weight loss greater than 10% within six months, and night sweats.¹¹ In addition, the patient experienced a sudden onset of bilateral leg weakness, resulting in difficulty walking. He also complained of persistent lower back pain for the past two months. One week before hospital admission, he could not hold his urine and bowel movements. Based on the literature, patient with lymphoma may

experienced chronic back pain or radicular pain progressing to spinal cord compression that may result in neurological deficits such as paresis, ataxia, and/or sensory disturbances with bowel and bladder incontinence. Patients may present with two phases of symptoms. In the first prodromal phase, the presentation may be localized pain in the back with radicular pain in the legs and abdomen that persists for several months to a year. This is followed by the second phase, characterized by spinal cord compression over two to eight weeks. Because most patients present with chronic back pain, it is most often misdiagnosed as a pathologic compression fracture, spinal infection or abscess, or metastatic disease. Such misdiagnoses can delay appropriate management.^{11,12}

Patients with primary vertebral lymphoma will generally complain of motor and sensory disorders related to spinal cord compression, including pain radiating to the lower legs, weakness of the lower limbs, numbness or hypoesthesia of the lower back, and impaired urination and defecation function.^{12,13}

Paraparesis is a clinical manifestation of diffuse large B-cell lymphoma and is a rare presentation in immunocompetent patients. Several different mechanisms may underlie the development of paraparesis in diffuse large B-cell lymphoma. First, central nervous system (CNS) involvement of a heterogeneous clinical phenotype is common to disease progression in intravascular lymphoma—a rare, aggressive, and notoriously difficult neoplasm. Malignant lymphoid cells proliferate within the lumen of capillaries and small blood vessels and may involve any organ in the body. Presentation sometimes includes paraparesis secondary to extensive longitudinal transverse myelitis or direct spinal disease. Second, primary extranodal CNS lymphomas may develop in the spinal cord at any level. This condition is rare, accounting for only 1% of primary CNS lymphomas, and so-called intramedullary lymphomas may cause paraparesis as a primary presentation. Third, primary extranodal lymphomas of bone involving the vertebrae or sacrum may secondarily involve the spinal cord, either by their growth or by causing pathologic fractures. Both are usually late manifestations of the disease. Fourth, diffuse large B-cell lymphoma isolated primary epidural lymphoma is rare, often diagnosed at laminectomy. The fifth mechanism is difficult to distinguish from spinal epidural lymphoma, the disease may arise in the paravertebral lymph nodes of the posterior mediastinum extending into adjacent tissues.¹⁴⁻¹⁷

The diagnosis of NHL is established based on anamnesis, physical examination, and supporting investigations. Supporting investigations were performed to confirm a definite diagnosis, through bone marrow biopsy and immunophenotyping, also imaging studies were conducted to determine tumor stages. Bone marrow is recommended as a part of the diagnostic workup in all patients with NHL.¹² Radiological examination can help to rule out other diseases and assess the extent of vertebral lymphoma disease. Plain X-ray examination is not very helpful, and currently, MRI is more widely used to assist in diagnosis.¹²

MRI is the imaging modality of choice for evaluating the central nervous system disorder, involving both in the brain and spinal canal. The advantage of MRI is providing better soft tissue resolution than CT-Scan. In addition, MRI has functional imaging capabilities to anatomical detail. In patients with primary vertebral lymphoma, MRI generally provides an image of incomplete destruction, vertebral corpus collapse, and filling of the vertebral corpus area by soft tissue that has an epidural component leading to compression or narrowing of the spinal canal. The administration of gadolinium contrast agents will produce relatively homogeneous enhancement in the lymphoma mass.¹¹ NHL spine can be isodense or hypodense lesions on T1-weighted images, and hyperintense on T2-weighted images with homogeneous enhancement after contrast administration.¹⁷

Table 1. MRI differences of TB spondylitis with metastasis or primary tumor¹⁸

Radiographic issue	Metastasis	Tuberculosis
Vertebral body destruction	Present	Present
Vertebral endplates	Normal	Irregular
Intervertebral discs	Preserved	Destroyed in later stages
Posterior elements	Pedicle destruction (as an early sign)	Uncommon
Abcess, Calcification	Absent	Present

In case, the result of biopsy showed a malignant round cell tumor, histomorphology tends to be non-Hodgkin's lymphoma, diffuse, large cell. Based on the literature, a malignant round cell tumor is an aggressive malignant tumor with a round cell, appearance with an increased nucleus-cytoplasm ratio. This group of neoplasms is characterized by small, round, and relatively undifferentiated cells.¹⁵⁻¹⁸

Diffuse large B-cell lymphoma (DLBCL) is a molecularly heterogeneous disease with multiple complex chromosome translocations and genetic abnormalities such as cytogenetics, and gene expression. This disease originates from B-cells where immunoglobulin genes undergo somatic mutations in the germinal centers of the lymph nodes. Diffuse large B-cell lymphoma (DLBCL) is an aggressive and the most common type of lymphoma, accounting for one-third of all cases. Diffuse large B-cell lymphoma can occur as primary lymph node disease or extranodal. More than 50% of patients will have extranodal involvement, most commonly in the bone marrow/bone marrow and digestive tract, each involved in 15–20% of patients.¹⁹⁻²²

Extranodal non-Hodgkin's lymphoma of the spine is very rare, occurring in about 5%. Spinal cord compression can occur in NHL patients. Due to its rarity and unclear clinical presentations, the diagnosis can be confused with tuberculous spondylitis, which is a more common disease. Treatment can be started immediately after the diagnosis is made because spinal non-Hodgkin's lymphoma has a poor prognosis.²³

The patients was diagnosed with stage IV-B non-Hodgkin's lymphoma according to the classification of non-Hodgkin's lymphoma stages based on Ann-Arbor staging.

Table 2. Ann Arbor staging systems¹⁶

Stage	Defining status
Stage I	Restricted to single lymph node region (I) or a single extranodal site (I-E)
Stage II	Two or more areas of nodal involvement on the same side of the diaphragm (II) or one or more lymph node regions with an extranodal site (II-E).
Stage III	Lymphatic involvement on both side of the diaphragm (III), possibly with an extranodal site (III-E), the spleen (III-S), or both (III-SE).
Stage IV	Liver, marrow, or other extensive extranodal disease.
Substage	
Substage E	Localized, extranodal disease.
Substage A	Absence of systemic signs.
Substage B	Presence of unexplained weight loss (10% in 6 month), and/or unexplained fever, and/or night sweat.

The results of supporting immunophenotype examinations demonstrated CK (-)/CD45 (+)/CD3 (+)/CD20 (+)/Ki67 (+) 80–90%, with the conclusion that the immunohistochemical staining pattern is more appropriate for non-Hodgkin lymphoma, diffuse, large cell derived from B-cells (CD20 positive). This results align with the theory that the

immunophenotype of DLBCL can be confirmed by histochemistry or flow cytometry. Tumor cells in DLBCL generally express pan B-cell antigens (CD19, CD20, CD22, CD79a), and CD45. 50–75% of tumors express surface or cytoplasmic monoclonal immunoglobulins (Ig), most often of the IgM isotype.

The most common treatments for patients with non-Hodgkin lymphoma include chemotherapy, radiotherapy, immunotherapy, stem cell transplantation, and, rarely, surgery. Chemo-immunotherapy with rituximab combined with chemotherapy is the preferred option.²¹

Radiation is the main treatment for early stages (I, II). Stage II with bulky disease, stages III, and IV are treated with chemotherapy along with immunotherapy, targeted therapy, and in some cases radiation therapy for the treatment of patients with diffuse large B-cell lymphoma (DLBCL).^{7,8,21}

Conclusions

Primary non-Hodgkin's lymphoma in the vertebrae/spine is a very rare malignancy with very limited literature references. Patients usually present with complaints of back pain and sensory and motor disorders according to the affected spinal cord segment. Generally, complaints arise due to compression or infiltration of the spinal cord by a mass. Histopathological examination with immunohistochemistry can help to establish the diagnosis and determine the subtype of the tumor. In this case, the patient also developed TB spondylitis, a chronic granulomatous inflammatory disease of the spine caused by *Mycobacterium tuberculosis*. Some patients will experience neurological deficits. If the *M. tuberculosis* bacterial infection affects the vertebral corpus, the damage will lead to spinal instability and disruption of the surrounding structures. Patients may experience paraparesis or tetraparesis due to compression of the spinal cord. The symptoms of this disease included back pain, kyphosis, and constitutional syndrome. However vertebral NHL and TB spondylitis showed similar symptoms and clinical features. For this reason, good multidisciplinary collaboration is needed in managing primary non-Hodgkin's lymphoma in the spine since it is a very rare case which often underdiagnosed/neglected and delayed treatment is associated with poor prognosis.

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The Role of Biologic Agent in the Management of Ankylosing Spondylitis: A Case Report

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Abstract

Background: Ankylosing spondylitis (AS) is a chronic immune-related arthritis primarily affecting the spine, sacroiliac joints, and surrounding tissues. The estimated incidence of AS ranges from 1.30–1.56 million in Europe and from 4.63–4.98 million in Asia. However, data on the current prevalence of AS in Indonesia remains limited. Various treatment modalities are available, one of them are biological agents that play a significant role in managing disease progression and preventing complications. **Case:** A 25-year-old male presented with a four-year history of chronic back pain. Laboratory results showed an elevated C-reactive protein (CRP) level of 31.20 mg/dl. Pelvic and thoracolumbar X-ray showed kyphotic deformity, bamboo spine, and dagger spine appearance. The patient was diagnosed with high disease activity ankylosing spondylitis (ASDAS-CRP: 2.9). Initial treatment with nonsteroidal anti-inflammatory drug (NSAID) alone did not result in clinical improvement. Due to the severity of disease activity, combination therapy using NSAID and a tumor necrosis factor (TNF) inhibitor was used, and reported to give satisfactory clinical response. Additionally, patient also underwent corrective spinal surgery due to severe deformity. **Conclusion:** TNF inhibitors are currently considered as the first-line biological therapy in the management of ankylosing spondylitis, due to their superior efficacy and safety in controlling disease progression compared to other biological agents.

Keywords: ankylosing spondylitis, therapy, biological agent, NSAID, TNF inhibitors

Abstrak

Latar Belakang: *Ankylosing spondylitis* (AS) adalah jenis radang sendi kronis yang berkaitan dengan sistem imun, utamanya menyerang sendi tulang belakang, sendi sakroiliaka, serta jaringan di sekitarnya. Insidensi AS di Eropa diperkirakan mencapai 1,30–1,56 juta kasus, sementara di Asia diperkirakan mencapai 4,63–4,98 juta kasus. Walaupun demikian, data mengenai prevalensi terkini AS di Indonesia masih terbatas. Terdapat berbagai modalitas terapi untuk AS, salah satunya menggunakan agen biologis yang berperan penting dalam mengendalikan progresivitas penyakit dan mencegah komplikasi. **Kasus:** Seorang laki-laki berusia 25 tahun datang dengan keluhan nyeri punggung kronis yang telah berlangsung selama empat tahun. Hasil pemeriksaan laboratorium menunjukkan peningkatan kadar *C-reactive protein* (CRP) sebesar 31,20 mg/dl. Hasil rontgen pelvis dan torakolumbal menunjukkan deformitas kifotik, gambaran *bamboo spine*, dan *dagger spine*. Pasien didiagnosis dengan *high disease activity ankylosing spondylitis* (ASDAS-CRP: 2,9). Terapi awal dengan obat antiinflamasi nonsteroid (OAINS) tunggal tidak menunjukkan perbaikan klinis. Mengingat tingginya tingkat aktivitas penyakit, pasien diberikan terapi kombinasi OAINS dan agen biologis berupa inhibitor *tumor necrosis factor* (TNF), yang dilaporkan memberikan respons klinis yang baik. Pasien juga menjalani tindakan pembedahan koreksi tulang belakang karena deformitas yang berat. **Kesimpulan:** Inhibitor TNF saat ini dipandang sebagai terapi

biologis lini pertama dalam tata laksana *ankylosing spondylitis*, karena menunjukkan efikasi dan keamanan yang lebih baik dalam mengendalikan progresivitas penyakit dibandingkan dengan agen biologis lainnya.

Kata kunci: *ankylosing spondylitis*, terapi, agen biologis, OAINS, inhibitor TNF

Introduction

Ankylosing spondylitis is a chronic immune-related form of arthritis that primarily affects the spinal and sacroiliac joints, as well as the surrounding tissues such as tendons and ligaments. Inflammation in this area can lead to fibrosis and calcification in severe cases, resulting in significant reduction of flexibility and fusion of the spine.^{1,2} Clinical manifestations of ankylosing spondylitis typically include progressive back pain and stiffness of the spine, although inflammatory signs may also appear in other locations including the hips, shoulders, and peripheral joints.^{3,4,5}

The estimated number of ankylosing spondylitis case ranges from 1.30–1.56 million in Europe and as high as 4.63–4.98 million in Asia. Currently, data regarding the prevalence of ankylosing spondylitis in Indonesia remains limited. Most ankylosing spondylitis cases begin before the age of 45, within the productive age range; therefore, the onset of ankylosing spondylitis is associated with a significant decrease in patients' quality of life.^{1,4}

Several treatment modalities are available for ankylosing spondylitis, including nonsteroidal anti-inflammatory drug (NSAID), conventional disease-modifying antirheumatic drug (DMARD); biological DMARD (bDMARD) such as tumor necrosis factor (TNF) inhibitors and interleukin-17A (IL-17A) inhibitors, as well as targeted synthetic DMARD like Janus kinase (JAK) inhibitors. In certain cases of ankylosing spondylitis, monotherapy using NSAID is insufficient, and combination therapy using NSAID and biological agents if often required. Biological agents play a significant role in the management of ankylosing spondylitis, particularly in preventing complications and controlling disease progression.^{6,7,8}

Case

A 25-year-old male presented with a chief complaint of back pain that had been ongoing for the past four years. The pain is primarily felt in the lower back, more pronounced in the morning upon waking, and accompanied by stiffness lasting approximately one hour. The pain also occurs at night during sleep, often causing sleep disturbances. The pain worsened with specific movements, including changes in position, prolonged sitting, standing upright, and lying in a supine position. Conversely, the pain was relieved by bending forward, lying down, or engaging in physical activity. Numbness and tingling sensations in the little finger and the sole of the right foot were also reported. There were no complaints of weakness in the lower limbs. Bowel and bladder function were also normal. The patient had no history of other chronic diseases. He reported regular use of etoricoxib, a nonsteroidal anti-inflammatory drug (NSAID), once daily, for the past year, following a previous diagnosis of arthritis.

On physical examination, the patient was alert and fully oriented (*compos mentis*). Vital signs were within normal limits, with blood pressure of 102/63 mmHg, pulse rate of 81 beats/minute (regular), respiratory rate of 18 breaths/minute, oxygen saturation of 98% on room air, and axillary temperature of 36.7°C. Other general physical examination finding was unremarkable. Focused examination of the lumbosacral region found a kyphotic deformity and midline tenderness at L5-S1.

Initial laboratory results of the patient showed a normal complete blood count with leukocytes $7.24 \times 10^3/\mu\text{l}$, hemoglobin 13.2 g/dl, hematocrit 42.0%, and platelets $413 \times 10^3/\mu\text{l}$. Inflammatory markers were elevated, with erythrocyte sedimentation rate (ESR) of 48.0 mm/hour and C-reactive protein (CRP) level of 31.20 mg/dl. Rheumatoid factor test result was negative. Renal function, liver function, and serum electrolytes were all within normal limits. The patient underwent thoracolumbar AP/lateral X-ray, which found characteristic findings supportive of ankylosing spondylitis, including “bamboo spine” and

“dagger spine” appearance. No evidence of vertebral compression, fracture, or spondylolisthesis in the thoracolumbar region (**Figure 1**). Radiological examination of the pelvis is also consistent with ankylosing spondylitis (**Figure 2**). Chest radiography showed no abnormalities, with normal pulmonary structures.

Initially, the patient was diagnosed with arthritis and treated with etoricoxib 90 mg once daily for approximately 1 year. However, due to persistent symptoms and inadequate clinical improvement, the patient was referred to out tertiary care center for further evaluation. Upon reassessment, the patient was diagnosed with high disease activity ankylosing spondylitis, as indicated by an ankylosing spondylitis disease activity score based on C-reactive protein (ASDAS-CRP) of 2.9.

The patient subsequently received routine injection of etanercept, a tumor necrosis factor (TNF) inhibitor, 50 mg weekly, accompanied by administration of NSAID using meloxicam 7.5 mg once daily. In addition, spinal surgery was performed to correct the severe spinal deformity. The patient has shown gradual improvement after surgery: he has begun walking in an upright position and a progressive reduction in back pain.

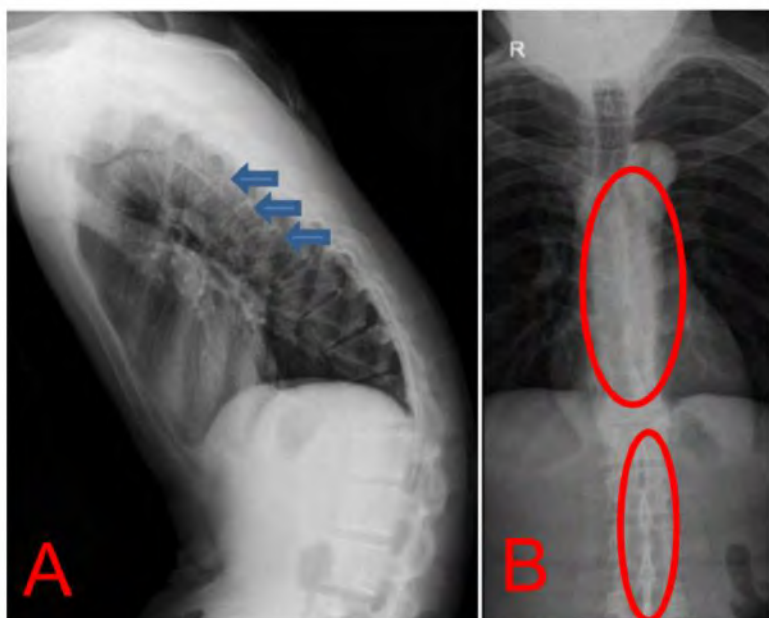


Figure 1. Radiological findings of AP/lateral X-ray of the thoracolumbar area showing kyphosis spine, with bamboo spine (blue arrow), and dagger spine (red circle).



Figure 2. Radiological findings of AP X-ray of pelvic area showing dagger spine (red circle).

Discussion

Ankylosing spondylitis is a chronic immune-related form of arthritis that primarily affects the spinal and sacroiliac joints, as well as the surrounding tissues such as tendons and ligaments. Ankylosing spondylitis is associated with significant morbidity, as it can lead to fibrosis and calcification of the spinal joints, resulting in significant reduction of flexibility and spinal fusion.¹⁻⁵

The hallmark clinical manifestations of ankylosing spondylitis are progressive back pain and spinal stiffness. However, signs of inflammation may also be found in other areas, including the hips, shoulders, and peripheral joints.¹⁻⁵ Peripheral arthritis in AS is usually presents acutely, asymmetrical, and often involves a few joints (oligoarticular pattern).^{6,9,10} Other common clinical features that should raise suspicion for ankylosing spondylitis include dactylitis, enthesitis, uveitis, psoriasis, and inflammatory bowel disease.⁶

Back pain associated with ankylosing spondylitis is typically located in the lower back and gluteal area. Onset of the disease usually occurs before the age of 45 and follows a chronically progressive course, persisting for more than three months. The pain often worsens at night and is accompanied by morning stiffness lasting more than an hour. The pain tends to improve with physical activity and worsen when rest.⁶ In this case, the patient is a 25-year-old male that presented with a complaint of chronic back pain persisting over the past four years. The pain lasted approximately one hour each morning, also occurred at night causing sleep disturbances, and was alleviated when the patient engaged in physical activity. Those clinical findings are aligned with the clinical features of ankylosing spondylitis.

Laboratory investigations found elevated inflammatory markers, including ESR and CRP. Radiological examination of the pelvis and thoracolumbar spine showed kyphotic deformity, “bamboo spine”, and “dagger spine” conditions. Thus, the patient was diagnosed with ankylosing spondylitis.

The clinical findings in patients are consistent with existing literature for diagnosis criteria of ankylosing spondylitis. Diagnosis of ankylosing spondylitis was made based on the Assessment of SpondyloArthritis International Society (ASAS)

classification criteria, which define spondyloarthritis in individuals with chronic low back pain (≥ 3 months), with onset before the age of 45, with or without peripheral manifestations, and accompanied by either sacroiliitis on imaging plus ≥ 1 feature of spondyloarthritis; and/or positive HLA-B27 results plus ≥ 2 features of spondyloarthritis. Sacroiliitis on imaging is defined by the presence of acute inflammation on magnetic resonance imaging (MRI), which is highly suggestive of sacroiliitis associated with spondyloarthritis, or definite radiographic sacroiliitis based on the modified New York criteria. Meanwhile, features of spondyloarthritis include: inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease/ulcerative colitis, a favorable response to NSAIDs, family history of spondyloarthritis, positive HLA-B27, and elevated CRP level.^{3,6,9,10}

Prior to the referral to our rheumatology clinic, the patient reported that his symptoms were only partially relieved by NSAID therapy, with the pain subsiding temporarily but never fully resolving. Given the suboptimal response to NSAID therapy and classification of the disease as high activity (ASDAS-CRP: 2.9), the patient was subsequently given TNF inhibitor agent (etanercept), in combination with NSAID (meloxicam).

The primary goal of ankylosing spondylitis management is to alleviate pain, prevent the progression of spinal rigidity and postural deformity, maintain functional mobility, as well as to minimize complications and disability. Pharmacological treatment options include NSAIDs, conventional disease-modifying antirheumatic drugs (DMARDs), biological DMARDs (bDMARDs) such as tumor necrosis factor (TNF) inhibitors and interleukin-17A (IL-17A) inhibitors, as well as targeted synthetic DMARDs. The first-line treatment for ankylosing spondylitis is continuous NSAID therapy. Conventional DMARDs may be considered in cases of peripheral manifestations, or if peripheral joint involvement constitute as the dominant symptom. The use of biological agents is indicated when there is inadequate response to NSAIDs after at least four weeks of therapy and if the level of disease activity remains high, defined by the ASDAS score of ≥ 2.1 . In such cases, combination therapy using NSAIDs and biologic agents (anti-TNF or anti-IL-17A) is recommended.

Following administration of biological agents, response to therapy should be evaluated within 12 months, using the ASDAS score. If the ASDAS score improves to < 1.3 (indicating inactive disease) or at least ≤ 2.1 (indicating low disease activity), continuation of the current biological therapy is recommended. However, if the ASDAS score remains ≥ 2.1 , it is recommended to switch the therapy to alternative biological agent, either within the anti-TNF class or to an IL-17A inhibitor.

Tumor necrosis factor (TNF) inhibitors are considered as the first-line biological agents in the management of ankylosing spondylitis, due to their superior efficacy and safety profile in slowing disease progression compared to other biological agents. Research shows that treatment with TNF inhibitors resulted in significantly better therapeutic response based on established outcome parameters, including ASAS20, ASAS 40, ASAS 5/6, and BASDAI50 scores.¹³

TNF inhibitors work by inhibiting the abnormal production of TNF, a proinflammatory cytokine that plays a central role in the pathogenesis of various inflammatory and autoimmune diseases, including ankylosing spondylitis. Etanercept, one of TNF inhibitors, is a genetically engineered dimeric fusion protein composed of the extracellular ligand-binding domain of the human TNF receptor-2 linked to the Fc portion of human IgG1. Etanercept prevents the binding of TNF to its receptor on the surface of cells, subsequently reducing inflammation.^{2,5,12} However, several contraindications must be considered prior to administration of TNF inhibitor, including tuberculosis and other active infections, heart failure, as well as malignancy.² Moreover, potential adverse reactions to biological agents that must be taken into account are also local injection site reactions, upper respiratory tract infections, headaches, and gastrointestinal disorders.^{2,5,12}

During TNF inhibitor therapy, the patient experienced a noticeable reduction in pain, and no adverse effects related to the administration of the biological agent were observed. However, the patient had already developed significant spinal

deformity prior to seeking treatment, which led to functional limitations in carrying out daily activities. Therefore, in addition to pharmacological treatment, the patient also underwent spinal surgery to address his spinal deformity. Delayed diagnosis and treatment of ankylosing spondylitis can lead to irreversible structural changes, including spinal deformities. Thoracolumbar kyphosis is reported in approximately 30% of ankylosing spondylitis cases.^{2,8} In such cases, surgical intervention such as osteotomy and spinal stabilization are required. The goal of surgical treatment is to restore normal spinal alignment, thereby improving patient's functional ability and quality of life.^{2,8}

Conclusion

A case of 25-year-old male diagnosed with ankylosing spondylitis has been presented. Diagnosis of ankylosing spondylitis was made based on the ASAS criteria. Following diagnosis, the patient was treated with a combination of NSAIDs and a biological agents (anti-TNF). The patient reported significant pain relief after initiation of therapy. However, due to preexisting spinal deformity, corrective spinal surgery was also performed to restore normal posture and function. TNF inhibitors are considered to have superior efficacy and safety in slowing disease progression of ankylosing spondylitis compared to other biological agents such as anti-IL-17A or targeted synthetic DMARD, like JAK-inhibitors. Early initiation of biological therapy in ankylosing spondylitis is crucial to reduce pain, prevent structural damage, and minimize long-term disability.

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Sebuah Kasus Pankreatitis Kronis pada Seorang Pria dengan Karsinoma Kaput Pankreas

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Abstrak

Pankreatitis kronis merupakan peradangan progresif pada pankreas yang dapat menyebabkan hilangnya fungsi eksokrin dan endokrin, dan dianggap sulit untuk diagnosis pada tahap awal. Sangat penting bagi dokter untuk memahami lebih jauh bagaimana mendiagnosis dan mengobati penyakit ini yang dapat memengaruhi kualitas hidup pasien dan mencegah komplikasi lebih lanjut.

Laporan kasus: Seorang pasien pria berusia 51 tahun, awalnya datang ke instalasi gawat darurat dengan keluhan utama nyeri epigastrium. Pasien juga mengeluhkan mata dan badan yang menguning disertai dengan urine berwarna kecokelatan serta feses pucat. Pasien mengaku mengalami penurunan berat badan yang tidak disengaja. Pada pemeriksaan fisik pasien ditemukan adanya konjungtiva yang ikterik. Hasil pemeriksaan laboratorium menunjukkan bahwa pasien memiliki tes fungsi hati yang abnormal dan ditemukan adanya peningkatan *tumor marker* CA 19-9. Setelah menjalani pemeriksaan *magnetic resonance cholangiopancreatography* (MRCP), dan berdasarkan data-data lain yang terkumpul, disimpulkan bahwa pasien mengalami karsinoma kaput pankreas dengan manifestasi klinis ikterus kolestatik. Pasien menjalani *endoscopic retrograde cholangiopancreatography* (ERCP) untuk melepaskan obstruksi kolestatik sehingga selanjutnya kondisi pasien berangsur membaik. Pada evaluasi berikutnya, pasien menjalani pemeriksaan *endoscopic ultrasound* (EUS), dan didapati pasien juga menderita pankreatitis kronis dengan beberapa batu di pankreas. Laporan kasus ini membahas pendekatan diagnostik dan pengobatan yang mungkin untuk dilakukan pada pasien dengan kondisi tersebut.

Kata kunci: pankreatitis kronis, kanker pankreas, ikterus kolestatik, batu pankreas

Abstract

Chronic pancreatitis is a progressive inflammatory disease of the pancreas which leads to loss of exocrine and endocrine function, and is considered difficult to diagnose in the early stage. It is crucial for physicians to have a deep understanding in diagnosed and treated the disease as this could affect the patient's quality of life and help to prevent further complications.

Case report: A 51-year-old male patient, presented to the emergency unit with epigastric pain. Patients also reported yellowing of the eyes and body, followed by dark-colored urine and pale stools. The patient also experienced unintentional weight loss. Physical examination indicated icteric conjunctiva. Laboratory test result demonstrated the patient had abnormal liver function test and elevated of tumor marker CA 19-9. After underwent magnetic resonance cholangiopancreatography (MRCP), and based on other collected clinical data, it was concluded that the patient had a pancreatic head carcinoma with cholestatic jaundice manifestation. Endoscopic retrograde cholangiopancreatography (ERCP) was performed to release the cholestatic obstruction, subsequently his condition was gradually improved. On follow-up evaluation, the patient underwent endoscopic ultrasonography (EUS) examination, and revealed to have chronic pancreatitis also with multiple

stones in the pancreas. This case report will discuss the diagnostic approach and possible treatment for the patient with such condition.

Keywords: chronic pancreatitis, pancreatic cancer, cholestatic jaundice, pancreatic stone

Pendahuluan

Pankreatitis kronis merupakan peradangan progresif yang mengakibatkan fibrosis dan kerusakan permanen pada pankreas sehingga dapat menyebabkan hilangnya fungsi eksokrin dan endokrin. Secara global, angka kejadian pankreatitis kronis termasuk jarang, yaitu berkisar antara 4,4–11,9 per 100.000 penduduk setiap tahunnya. Laki-laki mempunyai insidensi lebih tinggi yaitu 1,5–3 kali lipat dibandingkan dengan perempuan.¹

Untuk mendiagnosis pankreatitis kronis, dilakukan dengan memeriksa riwayat pasien, identifikasi faktor risiko, manifestasi klinis, serta dibantu dengan pemeriksaan penunjang seperti tes fungsi pankreas, pencitraan radiologi, dan endoskopi. Pankreatitis kronis pada tahap awal sangat sulit untuk dideteksi secara klinis dan pada pemeriksaan penunjang seringkali tidak menunjukkan gambaran gangguan fungsi pankreas dan radiologi yang terlihat. Secara klinis, pada umumnya penderita pankreatitis kronis mengeluhkan mual dan muntah, nyeri epigastrik yang menjalar ke punggung, dan penurunan berat badan yang tidak dapat dijelaskan. Apabila kondisi ini terus berlanjut, parenkim pankreas akan tergantikan dengan jaringan fibrosis yang kemudian dapat meningkatkan tekanan pada *common bile duct* (CBD) bahkan pasien akan mengalami striktur fibrotik periduktal. Jika hal ini terjadi, pasien dapat menunjukkan gejala dengan derajat yang beragam mulai dari asimtomatik, nyeri perut, sampai ikterus dan adanya gangguan hasil pemeriksaan tes fungsi hati.²

Laporan kasus ini membahas seorang pasien yang menunjukkan manifestasi klinis ikterus kolestasis dan setelah menjalani pemeriksaan lebih lanjut, pasien dinyatakan menderita karsinoma kaput pankreas. Dalam evaluasi lanjutan dengan *endoscopic ultrasonography* (EUS), juga ditemukan adanya gambaran pankreatitis kronis yang disebabkan oleh batu pankreas.

Hal ini menjadi menarik bagi penulis untuk membahas pankreatitis kronis yang termasuk jarang ditemukan, dengan harapan meningkatkan pengetahuan dan mendukung peningkatan kualitas pelayanan pasien secara klinis, baik dalam diagnosis maupun tata laksana penyakit ini.

Ilustrasi Kasus

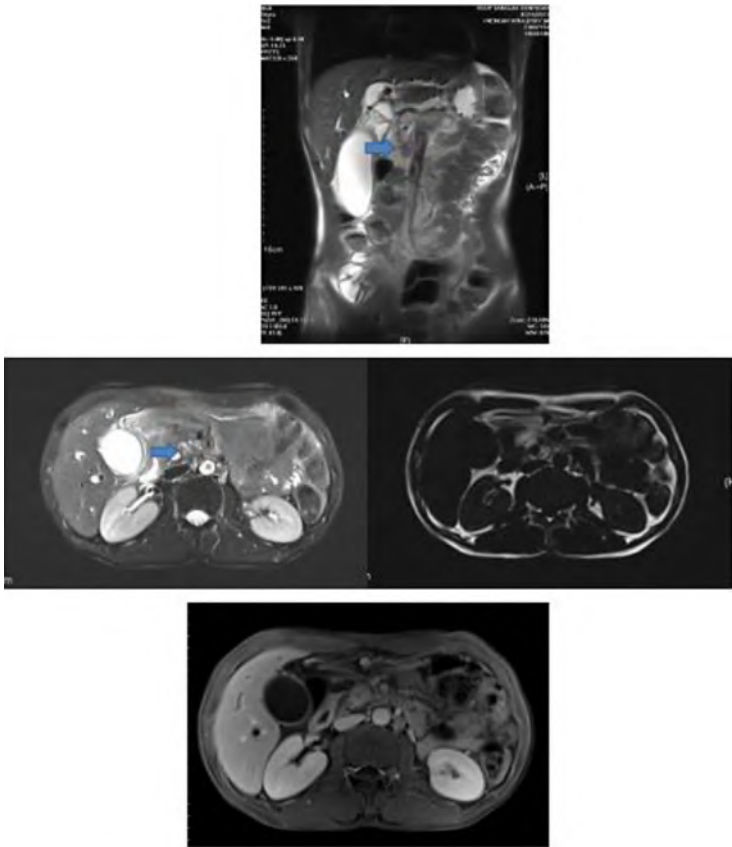
Seorang pasien laki-laki berusia 51 tahun, datang ke instalasi gawat darurat (IGD) RSUP Prof. Dr. I.G.N.G. Ngoerah pada 13 Februari 2023 dengan keluhan utama nyeri ulu hati yang dirasakan sejak 4 hari sebelum masuk rumah sakit. Nyeri ulu hati dilaporkan bersifat hilang timbul dan tidak menjalar. Pasien juga mengeluhkan bahwa mata dan tubuh menguning sejak 4 hari tersebut disertai dengan perubahan warna urine menjadi lebih pekat seperti teh, dan feses berwarna pucat seperti dempul. Pasien mengakui mengalami penurunan berat badan sekitar 15 kg yang baru disadari sejak 3–4 hari sebelum masuk rumah sakit. Didapatkan adanya riwayat minum alkohol dengan jumlah cukup banyak dalam kesehariannya, namun sudah berhenti sejak 10 tahun terakhir. Pasien juga memiliki riwayat menderita diabetes melitus tipe 2 (DMT2) dan baru mengonsumsi obat untuk mengontrol gula darah dalam 2 bulan terakhir ini, namun pasien tidak mengingat nama obat yang dikonsumsi. Riwayat penyakit lain seperti hepatitis, batu empedu, *autoimmune* disangkal oleh pasien. Pemeriksaan awal saat tiba di IGD, didapatkan kondisi pasien sadar penuh dengan tanda vital yang stabil.

Berdasarkan hasil pemeriksaan fisik, ditemukan adanya konjungtiva yang ikterik, bagian abdomen terkesan terdapat distensi abdomen dengan bising usus masih dalam batas normal, palpasi hepar dan lien tidak teraba dengan *traube space* yang timpani. Tidak ditemukan adanya asites serta nyeri tekan abdomen.

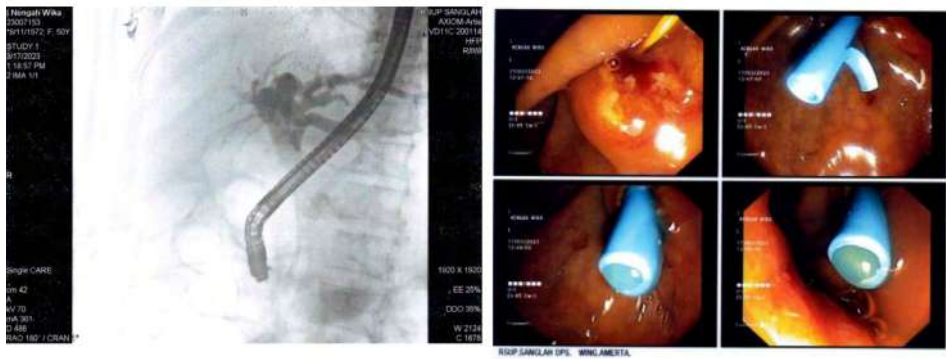
Hasil pemeriksaan laboratorium pada 13 Februari 2023 menunjukkan adanya peningkatan sel darah putih (*white blood cell*/WBC) dengan nilai $12,25 \times 10^3/\text{mcl}$ dan hasil hitung jenis dominan sel neutrofil sebesar $10,42 \times 10^3/\text{mcl}$. Pemeriksaan darah lengkap lainnya menunjukkan hasil yang normal yaitu hemoglobin 13,0 g/dl, hematokrit 37,2% dan trombosit $451 \times 10^3/\text{mcl}$. Kadar enzim transaminase pasien meningkat yaitu SGOT 85,1 U/l (nilai normal 5–34 U/l) dan SGPT 123,3 U/l (nilai normal 11–50 U/l). Kadar bilirubin pasien juga meningkat dengan total 31,7 mg/dl (nilai normal 0,3–1,2 mg/dl) terdiri dari bilirubin direk 22,46 mg/dl (nilai normal 0,0–0,5 mg/dl) dan bilirubin indirek 9,24 mg/dl. Kadar fosfatase alkali (*alkaline phosphatase*/ALP) pasien juga ditemukan tinggi yaitu sebesar 699 U/l (nilai normal 53–124 U/l), kadar *gamma glutamyl transferase* juga sangat meningkat sebesar 444 U/l (nilai normal 11–59 U/l). Pemeriksaan enzim amilase 35,2 U/l (nilai normal 25–125 U/l) dan lipase 4,0 U/l (nilai normal 13–60 U/l). Dilakukan pemeriksaan ulang pada 22 Juni 2023 dengan hasil amilase yang masih sama, yaitu sebesar 34,9 U/l dan lipase <4,0 U/l. Hasil pemeriksaan albumin sebesar 3,49 g/dl yang kemudian membaik pada 30 Agustus 2023 dengan hasil 3,8 g/dl. Pada 14 Februari 2023, dilakukan pemeriksaan *tumor marker* CA 19-9 didapatkan peningkatan yang signifikan yaitu sebesar 4422,93 U/ml (nilai normal 0,00 – 37,00 U/ml). Telah dilakukan penapisan virus hepatitis pada pasien dengan hasil HBsAg dan anti-HCV tidak reaktif.

Sebagai langkah penegakan diagnosis lebih lanjut, pada tanggal 16 Februari 2023 dilakukan pemeriksaan *magnetic resonance cholangiopancreatography* (MRCP) dan diperoleh hasil adanya pepadatan solid dengan intensitas heterogen, *irregular* berbatas sebagian tidak tegas, tepi *lobulated* pada kaput pankreas yang mendesak *common bile duct* (CBD) distal menyebabkan obstruksi parsial setinggi level tersebut, yang mendilatasi dari sisi proksimal CBD, *common hepatic duct* (CHD), hingga *hepatic duct* bagian kanan dan kiri, serta sisi distal *pancreatic duct*. Berdasarkan pemeriksaan tersebut, disimpulkan suspek *pancreatic ductal carcinoma*, dengan *hydrops gall bladder* dan organ lain seperti hepar, lien dan ginjal tak tampak kelainan (**Gambar 1**).

Hasil dari MRCP tersebut ditindaklanjuti dengan prosedur *endoscopic retrograde cholangiopancreatography* (ERCP) pada tanggal 17 Maret 2023. Pada *cholangiogram* ditemukan adanya pelebaran duktus bilier mulai dari CBD (1,86 cm), *common hepatic duct* dan *intrahepatic bile duct* (IHBD), sehingga disimpulkan bahwa pasien mengalami ikterus kolestasis yang disebabkan karsinoma kaput pankreas. Kemudian dilakukan sfingterotomi pada pasien yang dilanjutkan dengan pemasangan *stent* plastik 5 cm, 10 Fr. Cairan empedu disertai pus dilaporkan keluar dengan lancar dari *stent*, pascatindakan tidak ada perdarahan dan cairan empedu keluar dengan lancar. Berdasarkan hasil pemeriksaan di atas, pasien didiagnosis menderita karsinoma kaput pankreas.



Gambar 1. Hasil pemeriksaan MRCP abdomen pasien



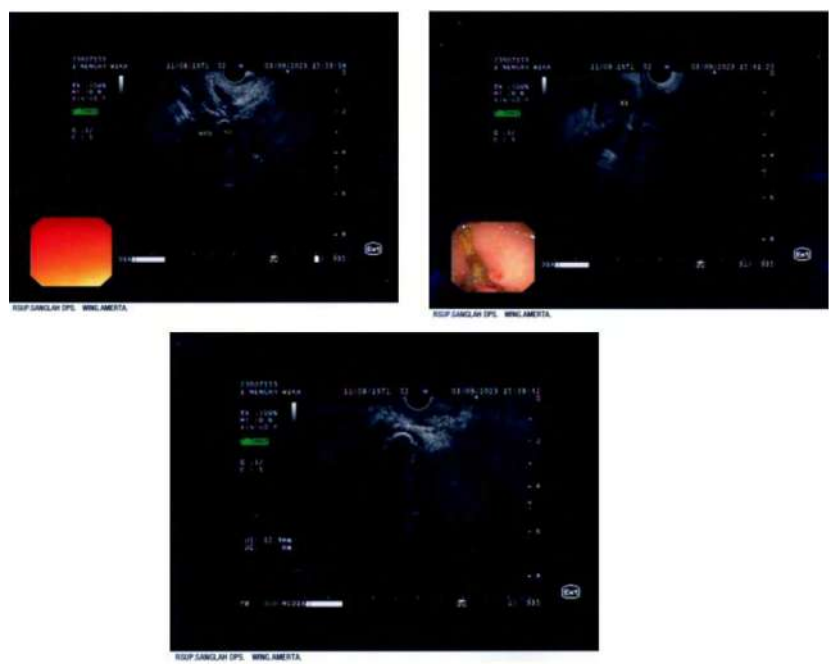
Gambar 2. Gambaran hasil tindakan *endoscopic retrograde cholangiopancreatography* (ERCP) 17 Maret 2023

Tabel 1. Hasil pemeriksaan serial terhadap bilirubin dan enzim transaminase

Parameter	13-2-2023	15-2-2023	18-6-2023	30-8-2023	Nilai normal
Bilirubin total	31,70	35,30	3,90	1,10	0,3–1,2 mg/dl
Bilirubin direk	22,46	25,25	2,81	0,51	0,0–0,5 mg/dl
Bilirubin indirek	9,24	10,05	1,09	0,59	0,3–0,7 mg/dl
SGOT	85,1	84,6	49,00	23,00	5–34 U/l
SGPT	123,30	60,80	56,00	16,00	11–50 U/l

Tindakan ERCP kedua dilakukan pada 22 Juni 2023 untuk melakukan prosedur pelepasan dan pemasangan kembali *stent* plastik karena pasien mengalami ikterus kolestasis berulang. Setelah menjalani ERCP kedua, pasien menunjukkan adanya perbaikan klinis dan laboratoris yang sangat baik. Pemeriksaan serial terhadap kadar bilirubin dan enzim transaminase dapat dilihat dalam **Tabel 1**. Pada 3 September 2023, pasien menjalani prosedur *endoscopic ultrasonography* (EUS) sebagai langkah evaluasi lanjutan.

Dari pemeriksaan tersebut ditemukan adanya batu multipel pada pankreas dengan ukuran terbesar 1,2 cm, duktus pankreas tampak melebar, parenkim pankreas tampak nekrosis. Kesimpulan dari pemeriksaan tersebut adalah pankreatitis kronis disertai batu multipel di pankreas. Setelah dilakukan EUS, disimpulkan bahwa selain menderita karsinoma kaput pankreas, pasien juga menderita pankreatitis kronis dengan batu multipel pada pankreasnya. Selanjutnya, pasien mendapatkan terapi suportif sementara berupa *paracetamol* 750 mg jika skala nyeri lebih dari 4, MST 10 mg bila skala nyeri lebih dari 6 dan *ursodeoxycholic acid* (UDCA) 250 mg tiap 8 jam secara rutin. Pasien juga direncanakan untuk penatalaksanaan lebih lanjut terkait kondisi terbaru pasien tersebut.



Gambar 3. Hasil pemeriksaan *endoscopic ultrasonography*

Diskusi

Pankreatitis kronis merupakan kerusakan *irreversible* pada parenkim pankreas dan sistem duktalnya yang disebabkan oleh inflamasi dalam jangka waktu panjang. Inflamasi tersebut menyebabkan terbentuknya fibrosis dan jaringan parut pada pankreas karena adanya faktor genetik, lingkungan, dan berbagai faktor risiko lainnya. Secara teoretis, terdapat lima mekanisme patofisiologi bagaimana pankreatitis kronis dapat terjadi.

Pertama, mekanisme “*two hit*” di mana *hit* pertama adalah episode pankreatitis akut lalu *hit* kedua merupakan respons inflamasi dari *hit* pertama yang mengaktivasi sel inflamasi dan profibrotik termasuk sel stelata pankreas. Kedua, pankreatitis kronis terjadi akibat episode pankreatitis akut berulang yang menyebabkan inflamasi dan aktivasi sel stelata pankreas dan menyebabkan terjadinya fibrosis. Ketiga, stres oksidatif akibat radikal bebas pada sel asinar yang menyebabkan oksidasi membran lipid dan ekspresi dari faktor transkripsi. Hal ini kemudian menyebabkan nekrosis sel asinar, aktivasi protease intravesikular dan fibrosis. Keempat, pengaruh langsung toksik metabolik akibat faktor lingkungan dan metabolitnya terhadap sel asinar yang menyebabkan inflamasi pada pankreas. Kelima, disfungsi duktal yang menyebabkan pembentukan sumbatan protein dan obstruksi duktal *upstream*. Diagnosis pankreatitis kronis, ditegakkan berdasarkan gabungan data antara lain dari riwayat pasien, manifestasi klinis, faktor risiko, serta pemeriksaan penunjang seperti tes fungsi pankreas, pencitraan radiologi, dan endoskopi. Namun, pankreatitis kronis pada tahap awal sulit untuk dideteksi dengan tidak adanya gambaran gangguan fungsi pankreas dan radiologis yang terlihat.²

Pada pankreatitis kronis, pasien umumnya mengeluhkan adanya mual dan muntah, nyeri epigastrik yang menjalar ke punggung, dan penurunan berat badan yang tidak dapat dijelaskan. Di tahapan yang lebih lanjut, parenkim pankreas akan tergantikan dengan jaringan fibrosis yang dapat meningkatkan tekanan pada *common bile duct* (CBD). Bahkan bila kondisi tersebut terus berlangsung pasien akan mengalami striktur fibrotik periduktal. Apabila hal ini terjadi, pasien dapat menunjukkan gejala mulai dari asimtomatik, nyeri perut, sampai ikterus dan gangguan hasil pemeriksaan tes fungsi hati. Gejala tersebut cukup selaras dengan gejala klinis yang dilaporkan pada kasus ini, meliputi nyeri perut, ikterus dan juga penurunan berat badan. Fungsi dari pankreas pasien juga terganggu dengan adanya penyakit diabetes melitus tipe 2 yang diderita pasien sejak 2 bulan terakhir sebelum pemeriksaan. Kondisi pankreatitis kronis memang dinyatakan dapat menyebabkan gangguan endokrin salah satunya adalah diabetes. Selain gangguan endokrin, fungsi eksokrin pankreas juga akan terganggu dan akan menimbulkan gejala seperti *steatorrhea*, malabsorpsi lemak, dan defisiensi vitamin larut lemak (vitamin A, D, E, K, B12) namun kondisi tersebut belum ditemukan pada pasien.²

Pasien mengakui adanya riwayat konsumsi alkohol saat usia muda. Alkohol memang dinyatakan sebagai faktor risiko yang paling umum pada kasus pankreatitis kronis. Sekitar 70% kasus pankreatitis kronis memiliki faktor risiko mengonsumsi alkohol. Sebuah studi analisis yang terdiri dari 14 penelitian kohort dengan 2.187 kasus kanker pankreas menyatakan bahwa konsumsi alkohol >30 g/hari dapat meningkatkan risiko seseorang untuk menderita kanker pankreas. Salah satu klasifikasi faktor risiko yang dapat digunakan untuk memasukkan ke dalam kategori faktor risiko pankreatitis kronis adalah M-ANNHEIM yang merupakan singkatan dari M (faktor risiko multipel), A (alkohol), N (nikotin), N (faktor nutrisi), H (herediter), E (faktor duktus eferen), I (faktor imunologis), M (*miscellaneous* atau faktor metabolik lainnya).^{2,3}

Pemeriksaan laboratorium pasien menunjukkan hasil kadar enzim amilase dan lipase masih dalam rentang normal yaitu 35,2 U/l untuk enzim amilase (nilai normal 25–125 U/l) dan 4,0 U/l untuk lipase (nilai normal 13–60 U/l) kemudian dilakukan pemeriksaan ulang pada 22 Juni 2023 dengan hasil kadar enzim amilase 34,9 U/l dan lipase <4,0 U/l. Secara teoretis, akibat tergantikannya jaringan pankreas dengan jaringan fibrotik yang berujung pada terjadinya kerusakan jaringan endokrin dan eksokrin pankreas, menyebabkan enzim pankreas yang awalnya normal atau bahkan di bawah batas normal menjadi pankreatitis kronis yang lanjut. Olesen *et al*, dalam sebuah penelitian yang melibatkan 121 pasien pankreatitis kronis menyatakan bahwa serum amilase di bawah 17,3 U/l memiliki spesifisitas 94% dan sensitivitas 59% dalam mendeteksi

pankreatitis kronis dan lebih menonjol pada kondisi penyakit yang sudah tahap lanjut.^{2,4}

Pada kasus ini, pasien mengalami peningkatan *tumor marker* CA 19-9 yaitu sebesar 4.422,93 U/ml (nilai normal 0,00–37,00 U/ml). Hal ini mungkin dapat memberikan kecurigaan bahwa kondisi pasien berkaitan dengan adanya keganasan. Telah diketahui bahwa CA 19-9 merupakan penanda biologis yang meningkat secara signifikan pada pasien kanker pankreas.⁵ Namun sebuah penelitian menunjukkan bahwa CA 19-9 sebenarnya juga berperan dalam menentukan prognosis dibandingkan dengan diagnosis pasien karena kapasitas prediksi positifnya hanya sebesar 57,1% pada pasien kanker pankreas. CA 19-9 dibentuk oleh jaringan parenkim pankreas normal dan traktus biliaris. Namun selain itu, ternyata penanda ini juga dihasilkan oleh sel epitel lambung, kolon, mukosa uterus, dan kelenjar saliva. Dalam kaitannya dengan keganasan, CA 19-9 meningkat pada keganasan lambung, kolorektal, paru-paru, tiroid, bilier dan pankreas. Selain keganasan, CA 19-9 juga dapat meningkat pada penyakit jinak pankreatobilieris seperti kolangitis, obstruktif *jaundice* dan pankreatitis. Kim Sunyoung *et al*, menyatakan bahwa pada pasien dengan peningkatan penanda tersebut, disarankan melakukan pemeriksaan *computed tomography* (CT) *scan* untuk mencari kemungkinan adanya keganasan terlebih dahulu. Pemeriksaan CA 19-9 secara berkala disarankan dilakukan apabila keganasan tidak ditemukan.⁶

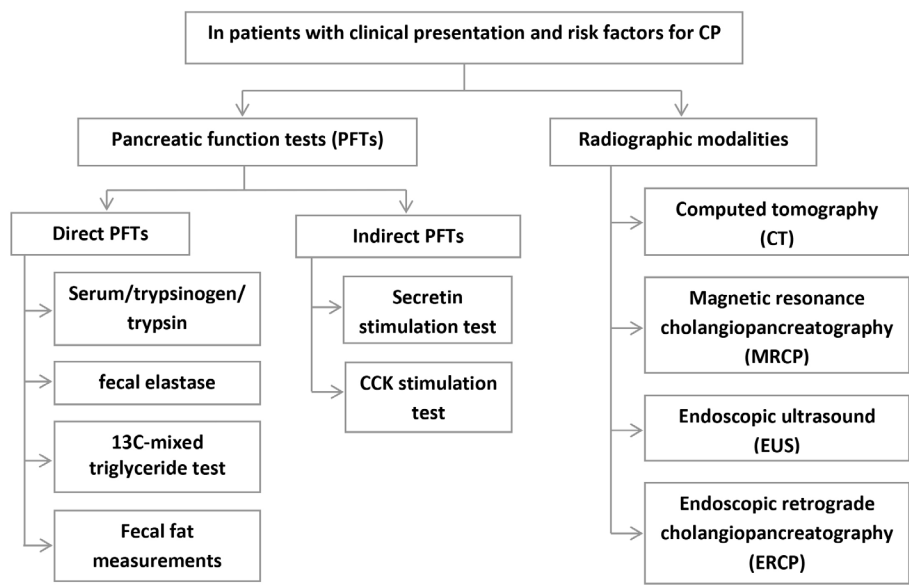
American College of Gastroenterology (ACG) merekomendasikan CT *scan*, MRI, atau MRCP sebagai pemeriksaan lini pertama untuk menegakkan diagnosis pankreatitis kronis. CT *scan* memiliki sensitivitas sebesar 74–90% dan spesifisitas 80–89% dalam mendiagnosis pankreatitis kronis.⁷ MRCP lebih baik dalam melakukan evaluasi parenkim pankreas dan perubahan duktal dibandingkan CT *scan*. Pada MRCP perubahan parenkim pankreas yang dapat ditemukan adalah atrofi pankreas, kontur *irreguler* pada kaput atau kauda pankreas, dan perlambatan kenaikan kontras di parenkim pankreas.⁸ Pada kasus ini, dari hasil MRCP pasien ditemukan adanya pematatan solid intensitas heterogen, *irregular* berbatas sebagian tidak tegas, tepi *lobulated* pada kaput pankreas yang mendesak *common bile duct* distal dan menyebabkan obstruksi parsial setinggi level tersebut, yang mendilatasi bagian proksimal *common bile duct*, *common hepatic duct*, hingga *hepatic duct* bagian kanan dan kiri, serta bagian distal *pancreatic duct*, suspek *pancreatic ductal carcinoma*, dengan *hydrops gall bladder*.²

Sebagai tindak lanjut dari hasil pemeriksaan MRCP tersebut pasien diputuskan untuk menjalani prosedur ERCP dan pemasangan *stent*. ERCP merupakan prosedur endoskopi yang menggunakan duodenoskop lapang pandang samping, yang memfasilitasi identifikasi ampula vater dan kanulasi sistem saluran empedu atau pankreas.⁹ ERCP berguna dalam pengobatan intervensi seperti ekstraksi batu dan pemasangan *stent*. Jika dilakukan perbandingan dalam mendeteksi kanker pankreas, sensitivitas MRCP sekitar 84% dibandingkan ERCP yang memiliki sensitivitas 70%, dan spesifisitasnya 97% dibandingkan ERCP yang memiliki spesifisitas 94%. MRCP juga lebih unggul dibandingkan ERCP dalam mendeteksi obstruksi total saluran pankreas. Namun, keuntungan ini tidak akan efektif bila diperlukan adanya intervensi terapeutik. ERCP masih menjadi prosedur pilihan apabila pasien kontraindikasi dengan MRCP dan memerlukan prosedur terapeutik.¹⁰ Berdasarkan hasil pemeriksaan-pemeriksaan tersebut, pasien dinyatakan menderita kanker kaput pankreas dengan kondisi ikterus kolestatik.

Setelah pasien menjalani prosedur ERCP sebanyak dua kali, kondisi pasien cenderung membaik, baik secara klinis maupun laboratoris. Kemudian dilakukan evaluasi lanjutan pada pasien dengan menggunakan EUS. Dari pemeriksaan tersebut ditemukan adanya batu multipel di pankreas dengan ukuran terbesar 1,2 cm, duktus pankreas melebar, parenkim pankreas tampak nekrosis dan tampak *stent* plastik di CBD. Berdasarkan pemeriksaan tersebut disimpulkan bahwa selain kanker kaput pankreas, pasien juga menderita pankreatitis kronis dan batu multipel di pankreas. Dibandingkan dengan CT *scan* dan MRCP, EUS merupakan modalitas pencitraan yang superior dalam penilaian parenkim pankreas dan perubahan sistem duktal. Penegakan diagnosis pankreatitis kronis juga dikatakan dapat terbantu dengan penggunaan EUS. Bahkan, EUS juga dapat mendeteksi komplikasi dari pankreatitis kronis misalnya striktur, batu, keganasan, dan membedakan

pankreatitis kronis dengan lesi pada pankreas lainnya.²

Untuk mengatasi adanya batu pada duktus pankreatikus yang diduga menjadi penyebab pankreatitis kronis yang diderita pasien, dalam *guideline* European Society of Gastrointestinal Endoscopy (ESGE) pada tahun 2018 direkomendasikan untuk menggunakan ERCP, sfingterotomi dan *baloon* atau dapat dengan menggunakan *extracorporeal shock wave lithotripsy* (ESWL). ESWL bertujuan untuk memecah batu menjadi ukuran <3 mm yang diharapkan dapat keluar secara spontan atau dikeluarkan melalui prosedur ERCP.²



Gambar 4. Pemeriksaan diagnostik pankreatitis kronis

Kedua kondisi pada pasien yaitu pankreatitis kronis dan kanker kaput pankreas memiliki prognosis yang berbeda. Tingkat kelangsungan hidup pasien pankreatitis kronis dalam 10 tahun ditunjukkan dengan angka kelangsungan hidup sebesar 70%, dan turun menjadi 45% dalam 20 tahun. Sedangkan pada pasien kanker pankreas, secara global angka kelangsungan hidup dalam 5 tahun adalah sekitar 6%. Faktor-faktor yang berdampak pada kelangsungan hidup meliputi usia, jenis kelamin, kualitas layanan kesehatan yang tersedia, adanya penyakit penyerta, dan gaya hidup.¹¹

Kesimpulan

Telah dilaporkan seorang pria berusia 51 tahun, terdiagnosis menderita kanker kaput pankreas dengan manifestasi klinis ikterus kolestatik yang kemudian mengalami perbaikan secara klinis maupun laboratoris. Pasien menjalani evaluasi kembali dengan EUS dan berdasarkan pemeriksaan tersebut, ditemukan adanya gambaran pankreatitis kronis disertai dengan batu multipel pankreas. Pankreatitis kronis memiliki manifestasi klinis yang beragam dan juga membutuhkan beberapa modalitas diagnostik untuk menetapkan diagnosis. Pada kasus ini dapat dilihat bahwa evaluasi terhadap manifestasi klinis yang didukung oleh pemeriksaan penunjang dengan tingkat akurasi yang tinggi dapat membantu untuk menegakkan diagnosis pankreatitis kronis pada pasien dengan karsinoma kaput pankreas.

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