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Case Report: Triple Negative Ulcerated Breast Cancer with Immunosuppressive Cold Tumor Environment

Iin Asriani[1], Andy Visi Kartika[2], M. Akram Chalid[3]
[1]Department of Medical Profession, Faculty of Medicine, Muslim University of Indonesia
[2]Department of Pathology Anatomy, Faculty of Medicine, Muslim University of Indonesia
[3]Department of General Surgery, Faculty of Medicine, Muslim University of Indonesia
Email: iinasriani25@gmail.com

Abstract. *Breast cancer is the most common malignancy among women worldwide according to Global Cancer Observatory (GLOBOCAN) data. One aggressive clinical form is ulcerative breast cancer, which is often categorized as locally advanced breast cancer (LABC). We report a case of a 42-year-old woman presenting with a left breast mass for 7 months that progressively developed into an ulcer with brownish, tea-colored discharge, without pain in the early phase and without systemic symptoms. Physical examination revealed an ulcerative mass with irregular margins, granulation tissue, and superficial collateral veins. Histopathological findings from FNAB and incisional biopsy confirmed invasive breast carcinoma of no special type (NST), WHO grade 3, with lymphovascular space invasion (LVSI+). Radiological evaluation showed no distant metastasis. The absence of pain and systemic inflammation in this case may be associated with the predominance of immunosuppressive cytokines such as IL-10 and TGF-β, which suppress nociceptor activation and systemic inflammatory responses, despite ongoing local inflammation. Management was carried out using a multimodal approach including supportive therapy, antibiotics, and planned mastectomy as definitive treatment. This case highlights the importance of clinical vigilance, as ulcerative breast cancer may progress without significant systemic symptoms.*

Keywords: *Ulcerative Breast Cancer, LABC, IL-10, TGF-β, Immune Evasion*

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INTRODUCTION

Breast cancer remains the most common malignancy in women worldwide. According to 2022 data from the Global Cancer Observatory (GLOBOCAN), breast cancer ranked first with 66,271 cases (30.1%). In Indonesia, the incidence of breast cancer reached 42.1 per 100,000 women, with a mortality rate of 16.6 per 100,000 women in 2020 (Islamyati & Suryati, 2023; Adhyatma & Nurlela, 2021; Pengsin & Meyasa, 2025).

Patients with breast abnormalities generally present with lumps. The appearance of these structural abnormalities is the result of a long process, from the initiation of genetic mutations to uncontrolled cell proliferation (Guerrini & Dobyns, 2014; Iffland & Crino, 2017; Niklinski et al., 2001; Hassanpour & Dehghani, 2017; Di et al., 2000). Ulcerative breast cancer has a more aggressive clinical progression than non-ulcerative types, characterized by rapid growth, tissue necrosis, and ulcer formation. This condition is often categorized as Locally Advanced Breast Cancer (LABC).

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Genetic mutations play a key role in the pathogenesis of breast cancer. BRCA1 and BRCA2 mutations are found in approximately 50% of hereditary breast cancer cases. In sporadic cases without a family history, somatic mutations, such as TP53 and PIK3CA, play a key role. Histopathology is the gold standard for establishing the diagnosis and determining the molecular subtype, which significantly influences treatment options. In highly progressive cases, such as ulcerative cases, surgical mastectomy is often the primary option (Velayutham et al., 2025).

CASE REPORT

A 42-year-old woman presented with a lump in her left breast seven months prior to hospitalization. Initially small, the lump resembled a corn kernel, it progressively enlarged without pain. The lump appeared reddish and felt warm. Four months prior to hospitalization, the lump ruptured, releasing a brownish, tea-like fluid that continuously oozed. In recent days, the fluid had become blood-tinged, foul-smelling, and painful.

The patient did not complain of fever, shortness of breath, headache, or other systemic symptoms. Her appetite was decreased, and she experienced sleep disturbances due to the pain. Physical examination revealed a good general condition with stable vital signs. She was malnourished, with a BMI of 17.3 kg/m^2. A local examination of the left breast revealed a lower quadrant mass with an ulcer, irregular edges, granulation tissue, minimal bleeding, hyperemia, and visible superficial collateral veins. Palpation revealed a warm, tender mass.

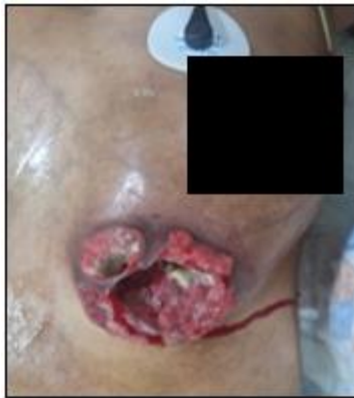

Figure 1. Clinical Photo of Left Breast 1

A large ulcer measuring approximately 5 cm in diameter, with an irregular shape and irregular borders is visible. The wound bed is composed of reddish granulation tissue, with a yellowish necrotic area filled with pus. The tissue bleeds easily and is filled with exudate. Dilated superficial veins and reddish skin are visible around the ulcer.

Laboratory tests were within normal limits (WBC 9.1 × 10^3/μL; GDS 135 mg/dL), indicating no systemic infection. FNAB examination showed mammary adenocarcinoma. Incisional biopsy confirmed invasive breast carcinoma of no special type (NST), WHO Grade 3, with lymphovascular space invasion (LVSI +) with HER-2 -, ER -, PR - subtypes, and high Ki-67 expression. Chest X-ray examination showed no metastasis. The patient received initial therapy with antibiotics (cefuroxime axetil and metronidazole), analgesics, and supportive therapy. A mastectomy was planned as definitive therapy.

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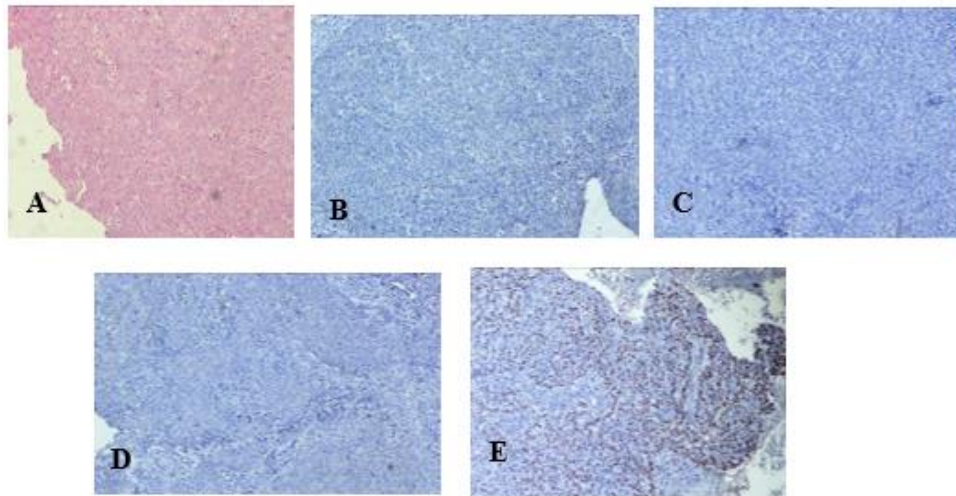

Figure 2. Microscopic Image Of Breast Tissue Biopsy 2

Microscopic image of triple negative subtype ulcerative breast cancer biopsy (A) HE staining depicts breast tissue of origin covered by skin epidermis tissue, some of which appear normal and without any particular abnormalities and others appear ulcerated. In the dermis layer, there are nests of malignant tumors originating from the mammary gland epithelium that invade the surrounding connective tissue stroma; (B) HER-2 negative receptor protein is not stained on the membrane of tumor cells and does not form a continuous pattern (Honey Comb Appearance); (C) ER negative with the presentation of receptor protein stained in the tumor cell nucleus <1%; (D) PR negative with the presentation of receptor protein stained in the tumor cell nucleus <1%; (E) Ki-67 high expression with the presentation of protein stained in the tumor cell nucleus 90% (>20%).

DISCUSSION

Breast cancer is the most common malignant condition in women. Non-luminal breast cancer subtypes (triple-negative breast cancer) have varying degrees of progression (Hashmi et al., 2018; Cejalvo et al., 2018; Kimbung et al., 2015; Abdelhafiz et al., 2021). Early diagnosis and appropriate treatment can improve the prognosis. This case report illustrates the progression of massive ulcerative breast cancer without systemic inflammation, clinically evident in fever or laboratory markers, such as the absence of elevated leukocyte counts, which are common in inflammatory cases. Breast cancer ulcers result from tumor cell infiltration into the dermis and blood vessels, leading to tissue ischemia, necrosis, and ultimately the formation of an open wound (Milam et al., 2021; Sundaram et al., 2018; Firmino et al., 2021; Brnić et al., 2025). Inflammation occurs locally, and cancer cells act like normal cells in the body by releasing cytokines such as IL-10, TGF-β, and IL-6, thus preventing cancer cell elimination by the immune system and allowing the cancer cells to spread more aggressively, also known as immune evasion.

The clinical finding of tea-like discharge suggests that the involved processes include necrosis due to disruption of tissue blood vessels, prolonged bleeding, and local inflammation. Severe clinical findings do not result in systemic disturbances in the patient, as evidenced by stable vital signs and the absence of systemic inflammatory markers, such as leukocytosis, which are common (Macaron et al., 2022; Zotova et al., 2023). Inflammation generally activates the body's defenses, releasing pro-inflammatory cytokines and migrating immune cells to the affected tissue. The absence of systemic signs of inflammation does not correlate with the absence of pro-inflammatory cytokines such as IL-6 or TNF-α in ulcerative breast cancer. These cytokine activation persists and plays a local role in ulcerative progression. Resistance to chemotherapy can also occur through TNF-α stimulation, which increases TAZ, a transcriptional coactivator in the Hippo pathway, thereby increasing cancer-initiating cells (Ciurescu et al., 2025).

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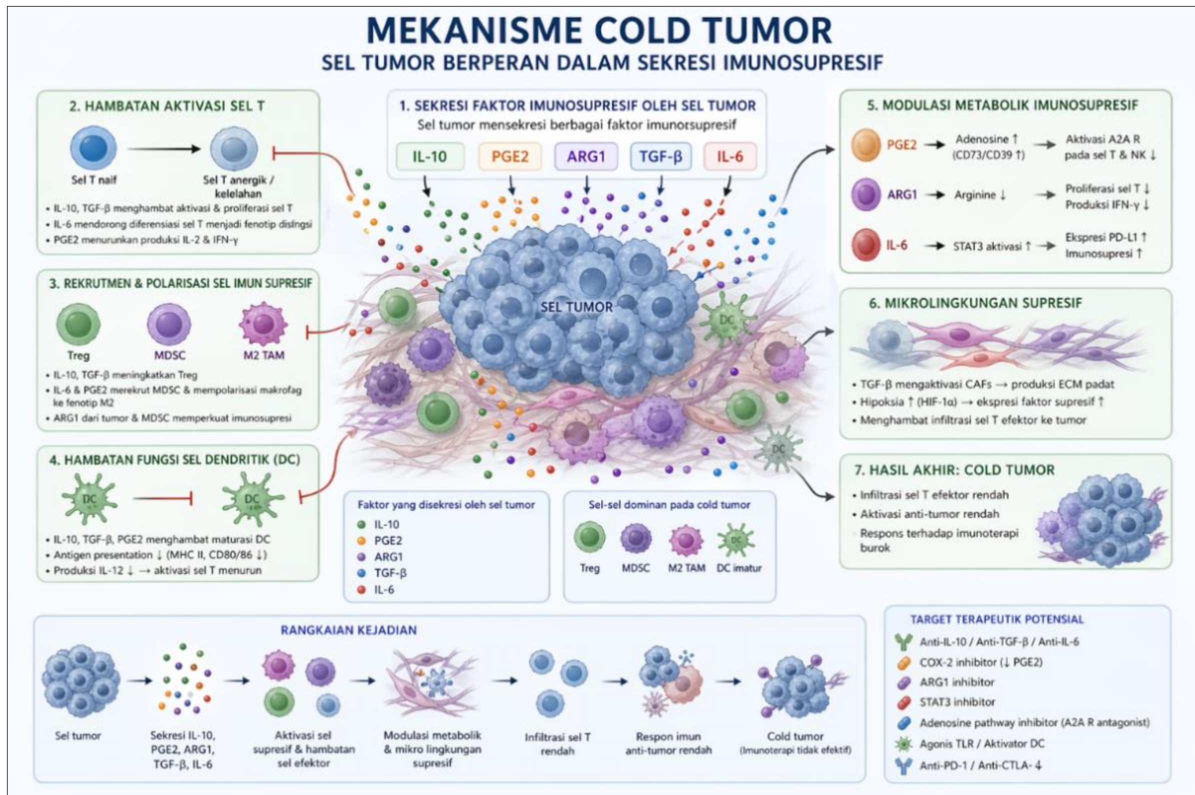

Figure 3. The Role of Cold Tumors in Immunosuppressive Secretion

The mechanism of cold tumor microenvironment formation, where tumor cells play an active role in creating immunosuppressive conditions. Tumor cells secrete various factors such as IL-10, TGF-β, IL-6, PGE2, and ARG1, which function to inhibit the activation and proliferation of effector T cells. Furthermore, there is recruitment and polarization of suppressive immune cells such as regulatory T cells (Treg), myeloid-derived suppressor cells (MDSC), and tumor-associated macrophages (TAM type M2). These factors also inhibit dendritic cell function, thereby decreasing antigen presentation. Simultaneously, metabolic modulation occurs (via the adenosine, arginine, and STAT3 pathways) which further suppresses the immune response. Hypoxic conditions in the tumor microenvironment also amplify the immunosuppressive effect. As a result, T cell infiltration into the tumor is low and the antitumor immune response is ineffective, resulting in a "cold tumor" condition characterized by low immune activity. (IL- (Interleukin-); TGF- β (Transforming Growth Factor-beta); PGE2 (Prostaglandin E2); ARG1 (Arginase 1); STAT3 (Signal Transducer and Activator of Transcription 3))

Chronic inflammation persists locally, causing extensive necrosis of breast tissue without pain. Immunosuppression produced by breast cancer inhibits the activation of nociceptors, preventing pain from being felt by patients, even when tissue damage is severe. Tissue adaptation in the early stages of cancer and the absence of nerve involvement also play a role. Therefore, pain becomes a symptom in advanced stages of breast cancer. IL-10 and TGF-β produced by cancer cells cause the local ulcerative environment to become dominated by anti-inflammatory cytokines. This suppresses pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1, which are key pain modulators (Habanjar et al., 2023).

Immunosuppressive cytokines such as IL-10 and TGF-β increase, leading to immune evasion and T-cell exhaustion. This can create an environment favorable for cancer cell growth. Progression can be aggressive, increasing the risk of metastasis, particularly through the lymphatic system (Alitalo & Detmar, 2012; Mumprecht & Detmar, 2009; Karaman & Detmar, 2014; Leber & Efferth, 2009; Klein, 2020). Therefore, in breast cancer, pro-inflammatory cytokines are not used to stimulate systemic inflammation but rather play a role in

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microinflammation or local inflammation in breast cancer, which is used to increase the progressive invasion of breast cancer (Imani et al., 2025).

Referring to Figure 3, the anti-inflammatory cytokine IL-10 activates STAT3 (Signal Transducer and Activator of Transcription 3) signaling in immune cells such as dendritic cells and macrophages, thereby reducing the immune response to tumor growth. IL-10-mediated STAT3 stimulates M2 macrophages, which promote angiogenesis and tumor progression. IL-6, produced by local inflammation and tumor cells, along with growth factors, plays a role in activating STAT3 signaling, which plays a role in stimulating pro-survival pathways and preventing apoptosis in cancer cells (Lv & Ding, 2025; Rašková et al., 2022).

Systemic symptoms in this case were not prominent, which could complicate the diagnosis. A comprehensive examination is essential to support the diagnosis and select the appropriate therapeutic approach. Physical findings, such as superficial collateral veins, are a key indicator of whether the cancer has invaded breast tissue, whether the tumor is large, or whether metastases have occurred in the mediastinum. Compression of blood vessels by tumor cells can cause a variety of symptoms, including edema of the face, neck, and surrounding tissues, shortness of breath, coughing, and hoarseness. However, in this case, no severe vena cava compression or superficial vena cava syndrome was found (Chow et al., 2024).

Table 1. Breast Cancer Stage Grouping Based on The TNM (Tumor-Node-Metastasis) System

Anatomic Stage			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N**	M0
	T1*	N1**	M0
	T2	N1**	M0
Stage IIB	T2	N0	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Referring to Table 1, the clinical findings in this case can be categorized as stage IIIB. There is chest wall skin invasion accompanied by local inflammation or ulceration (T4). There is no regional lymph node involvement, either enlarged or tender, such as in the axillary or subclavian regions (N0). Distant organ metastasis has not been detected, as evidenced by radiological investigation results, such as a chest x-ray, which showed results within normal limits. An increased risk of metastasis is assessed by the finding of lymphovascular space invasion (LVSI+). Staging is important for determining the appropriate therapeutic approach. In cases of stage IIIB breast cancer with locally advanced breast cancer or ulceration, determining the resection margin is difficult. Surgical procedures, such as a mastectomy with wide resection, can be performed after initial therapy with neoadjuvant chemotherapy (Ma et al., 2025; Decker et al., 2012; O'Halloran et al., 2019; Buchholz et al., 2003; King & Morrow, 2015; Asselain et al., 2018; Ring et al., 2003).

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Histopathological examination indicates the cancer belongs to the triple-negative subtype. Aggressive cell proliferation and reduced cell apoptosis occur. This is influenced by its molecular characteristics, which involve the activation of cell signaling pathways, such as the MAPK pathway, which contributes to stimulating cancer cell proliferation and growth. Meanwhile, the PI3K-AKT pathway plays a role in protecting cancer cells from apoptosis or cell survival, maintaining metabolic stability and the progression of the cancer cell cycle (Kerr et al., 2016; Pan et al., 2024).

Therapeutic approaches such as radiotherapy or systemic chemotherapy aimed at shrinking the cancer and preventing organ metastasis may be considered due to the rapid progression of ulcerative breast cancer (Wang & Wu, 2023; Cheng & Ueno, 2012; Redig & McAllister, 2013). Targeted therapy in this case can inhibit cancer cell growth through the inhibition of superficial monoclonal antibodies. Neoadjuvant chemotherapy can reduce the risk of vena cava syndrome by inhibiting cancer growth and shrinking the cancer, although it does not have a significant effect. This therapy is often given as initial therapy before surgical mastectomy.

Treatment for this patient includes administration of antibiotics in the form of cefuroxime axetil and metronidazole (Manka et al., 2000). This antibiotic combination aims to address possible aerobic and anaerobic bacterial infections in the ulcerative wound. In addition, symptomatic therapy is provided, including analgesics for pain relief and gastric protection medications. Initial management also includes an incisional biopsy to confirm the histopathological diagnosis before definitive therapy is initiated (Rastogi, 2018; Birgin et al., 2020; Rao et al., 2020; Magro et al., 2013). A mastectomy, a surgical procedure that removes the affected breast tissue, is planned. In cases of breast cancer with skin ulceration or extensive local tissue involvement, mastectomy is often the primary treatment option for locally advanced breast cancer. The approach to breast cancer therapy is generally multimodal and may include surgery, chemotherapy, radiotherapy, and targeted therapy, depending on the stage and biologic characteristics of the tumor (Chabner, B. A., & Longo, 2015).

CONCLUSION

Ulcerative breast cancer is a malignancy with rapid progression and extensive local tissue involvement. The absence of pain and systemic inflammatory symptoms does not rule out disease severity, as the inflammatory process in cancer is predominantly local, with the contribution of an immunosuppressive environment mediated by cytokines such as IL-10 and TGF-β. A comprehensive diagnostic approach, including histopathological examination and molecular subtype assessment, is crucial in determining therapeutic strategies. Appropriate and multimodal management, including surgery, is necessary to improve clinical outcomes in ulcerative breast cancer.

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