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**Case Report / Приказ болесника**

Aleksandar Guzijan<sup>1,†</sup>, Radoslav Gajanin<sup>1,2</sup>, Božana Babić<sup>1</sup>, Vesna Gajanin<sup>2</sup>, Bojan Jovanić<sup>1</sup>

**The breast necrosis caused by oral anticoagulant therapy**

Некроза дојке узрокована оралном антикоагулантном терапијом

<sup>1</sup>University Clinical Center of the Republic of Srpska, Banja Luka, Republic of Srpska, Bosnia and Herzegovina;

<sup>2</sup>University of Banja Luka, Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

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**†Correspondence to:**

Aleksandar GUZIJEAN

Breast Center, University Clinical Center of the Republic of Srpska, Dvanaest beba 1, 78000 Banja Luka, Republic of Srpska, Bosnia and Herzegovina

E-mail: [guzijan@hotmail.com](mailto:guzijan@hotmail.com); [aleksandar.guzijan@kc-bl.com](mailto:aleksandar.guzijan@kc-bl.com)

## The breast necrosis caused by oral anticoagulant therapy

### Некроза дојке узрокована оралном антикоагулантном терапијом

#### SUMMARY

**Introduction** Described in 1943 for the first time, breast necrosis during anticoagulant therapy is only rarely encountered in clinical practice.

The aim of the article is to described patient who used anticoagulant therapy and developed the breast necrosis during therapy.

**Case outline** A 57-year-old female patient was admitted to hospital with pain in her left breast, which examination showed to be erythematous, swelling, and hard. She had started experiencing the symptoms a few days before, and she denied having had a fever. Over the previous four weeks she had received anticoagulant treatment (Acenocoumarol) as popliteal embolectomy prophylaxis. The breast was firm, edematous, of limited mobility, and with no pectoral muscle infiltration. The breast ultrasound showed a homogeneous mass, with no signs of fluid retention or suspicious lesions. Upon admission, the patient began receiving intravenous antibiotic treatment and underwent blood tests. The second day upon admission, the patient's breast revealed a clearly demarcated area of necrotic skin. Surgical treatment was indicated. The surgery was performed in two stages, of which the first included a partial resection of the necrotic breast tissue, and the second simplex mastectomy. Histological analysis showed severe superficial necrosis, with underlying diffuse deep venous thrombosis and marked arteritis of medium and small vessels. Focal areas of extensive necrosis were found deep in the breast parenchyma.

**Conclusion** Considering that breast necrosis is extremely rare, it is usually not suspected initially. Learning about the patient's undergoing anticoagulant therapy is of crucial importance for giving the right diagnosis. Breast abscesses should also be ruled out. Surgery is the treatment of choice, as changes to the breast tissue are usually irreversible.

**Keywords:** anticoagulants; necrosis; gangrene; breast; hemorrhagic

#### САЖЕТАК

**Увод** Некроза дојке као последица примене антикоагулантне терапије је изузетно ретка појава у клиничкој пракси. Први случај у литератури описан је 1943. године.

Циљ рада је приказ пацијенткиње која је под антикоагулантном терапијом развила клиничку слику некрозе дојке.

**Приказ болесника** Пацијенткиња старости 57 година примљена је на клинику са болном и клинички увећаном, еритематозном и напетом левом дојком. Тегобе трају уназад пар дана, негира фебрилност. Анамнестички наводи оралну антикоагулантну терапију (Аценокумарол) уназад четири седмице, која је укључена након урађене транспоплитеалне емболектомије. Дојка тврда и едематозна, делимично покретна и без знакова инфилтрације пекторалног мишића. Ултрасонографски без издвајања слободне течности и суспектних солидних промена. По пријему је укључена парентерална антибиотска терапија и урађена иницијална лабораторијска обрада. Други дан по пријему долази до демаркације зоне некрозе на кожи леве дојке. Индикује се хируршки третман. Оперативни захват је урађен у два акта, први са парцијалном ресекцијом некротичног ткива дојке, а други са тоталном аблацијом остатка леве дојке. Хистолошки налаз је показао суперфицијалну некрозу са поткожном дифузном венском тромбозом на артеријама и крвним судовима мале и средње величине. Фокално се верификовала екстензивна некроза у паренхиму дојке.

**Закључак** С обзиром на то да је појава некрозе дојке изузетно ретка, најчешће се иницијално и не мисли на овај ентитет. Податак о антикоагулантној терапији је кључан у постављању сумње на ово обољење. Диференцијално дијагностички се мора мислити и на апсцес дојке. Начин лечења је примарно хируршки, промене настале у дојци су најчешће ирверзибилне.

**Кључне речи** антикоагулантна терапија; некроза; гангрена; дојка; хеморагија

## INTRODUCTION

Breast necrosis and breast gangrene are synonyms for a condition which is rarely encountered in clinical practice. Breast necrosis was first described by Cutler in 1924 [1]. Flood et al. was the first to write about a case of breast necrosis caused by oral anticoagulant therapy [1]. Apart from the breast being affected, medical literature mentions the same condition manifesting as tissue necrosis affecting thighs, fingers and toes, the face, the back, and other locales. In 35% of all the cases described necrosis was multifocal. According to the existing literature, 15% of all cases of necrosis associated with the administration of

anticoagulant therapy concerned breast tissue [2, 3]. In 1952, Verhagen wrote about soft tissue necrosis resulting from the administration of anticoagulant therapy, reporting a total of 13 cases, of which in one case breast tissue was affected [4]. In 1971, Hagensen described a case of necrosis of breast fibroadenoma as a distinct clinical and pathological entity [1]. Oral anticoagulant therapy is commonly given as venous thromboembolism treatment and prophylaxis. Searching the available databases (PubMed/MEDLINE) yielded around 40 published articles reporting on cases of breast necrosis caused by oral anticoagulant therapy. The illness develops suddenly and is accompanied with acute pain. The patient's clinical condition indicates an emergency. The patient's confirmation that she had been receiving anticoagulant therapy is extremely important, as it suggests the possibility of breast necrosis. Breast necrosis is progressive and leads to dry breast gangrene. The causes of breast necrosis remain unclear [1, 2, 5]. The sporadic cases that cannot supply enough data about the nature of this rare phenomenon [6].

## CASE REPORT

A 57-year-old female patient was admitted to hospital with symptoms indicating a problem in the left breast. The symptoms had unexpectedly appeared several days before. The patient complained about her left breast being painful, red, and swollen. In providing medical history information, the patient reported being on anticoagulant therapy (Acenocoumarol, 1 mg per day) for a month, during which she had not checked her INR value (International Normalized Ratio), as instructed by her vascular surgeon. The patient began receiving thromboembolism prophylaxis after a popliteal artery embolectomy. She also reported having developed a rectal cancer, which had been removed surgically. The patient had undergone rectum resection nine months earlier.

Upon admission, the patient's left breast was very swollen, erythematous, with the tissue feeling hard throughout and showing no signs of fluctuation (Figure 1).

Upon admission to hospital, the patient began receiving parenteral antibiotic and analgesic therapy. Her INR was tested, yielding 1.16. Following a consultation with a vascular surgeon, the patient was taken off anticoagulant therapy (Acenocoumarol), which was replaced with low-molecular-weight heparin (Enoxaparin sodium, 20 mg). Basic blood chemistry tests were done. Blood count values: WBC  $8.5 \times 10^9/L$ , RBC  $3.8 \times 10^{12}/L$ , HGB 108

g/L, HCT 0.341, PLT 341; biochemistry tests: Glucose 7.2 mmol/L, BUN 3.2 mmol/L, Creatinine 59 mmol/L, total protein 61.7 g/L, total bilirubin 9.8 mmol/L, direct bilirubin 2.8 mmol/L, AST 17 U/L, ALT 5 U/L, LD 202 U/L, GGT 58.8 U/L; electrolytes: Na 134.8 mmol/L, K 3.25 mmol/L, Cl 95 mmol/L, Ca 2.2 mmol/L, P 0.9 mmol/L. A radiologist was consulted, who performed a breast ultrasound, which confirmed the presence of edema and homogeneous breast mass, with no fluid accumulation or visible suspect solid or cystic lesions. The ultrasound examination revealed no pectoral muscle infiltration. On day 2 after the patient was admitted to hospital, an area of necrotic tissue on her left breast became clearly demarcated (Figure 2). Surgery was indicated, and the operative procedure performed involved partial resection of the left breast and necrectomy. Partial resection of the breast was performed because mastectomy, which was surgically performable, would have left a skin defect and made impossible closure by primary intent. Following the surgery, the edema in the left breast decreased in size, in parallel with intravenous continuous analgesia and regular blood tests (Electrolytes, INR). Post-operatively, the edema in the rest of the left breast reduced, making it possible to undertake a second surgical procedure and closure by primary intent. Next, the patient underwent mastectomy with closure by primary intent. The wound became infected post-operatively, but was successfully treated after an antibiotic sensitivity test was done and the best antibiotic regimen chosen.

Based on histopathological analysis, the patient was diagnosed with hemorrhagic infarct of the breast skin, subcutaneous tissue and parenchyma, as well as arterial thrombosis of the breast. Histological examination showed a loss of cellular detail in the skin and subcutaneous tissue of the breast (Figure 3), as well as small areas of haemorrhage and necrosis that engulfed glands and stromal breast tissue. In addition to superficial necrosis places were present much wider areas of necrosis of the breast parenchyma (Figure 4). Spotting and diffuse subcutaneous venous thrombosis in the arteries and blood vessels of small and medium size and also distended veins in deeper tissues with thrombi (Figure 5). Inflammatory changes were seen within and surrounding the wall of small arteries and some contained fibrin thrombi. Chronic edema and infiltrates are observed in the dermis and acute inflammation inside walls of numerous small arteries. The patient made a recovery and was discharged from hospital after 26 days.

## DISCUSSION

On average, the risk of breast necrosis among patients receiving anticoagulant therapy ranges between 0.01–0.1% [2]. As for the cases of breast necrosis, i.e. breast gangrene caused by oral anticoagulant therapy described in medical literature, the condition generally appeared shortly after patients began receiving oral anticoagulant therapy [1, 4, 7]. The severe complication of anticoagulant therapy is hemorrhagic skin necrosis [8]. In the majority of cases, this period was 3-6 days, although in some of the cases breast necrosis developed 15 years after the patients received anticoagulant therapy [9]. In our case, the condition began 4 weeks after oral anticoagulant therapy administration. Some of the cases describing breast necrosis involved low-molecular-weight heparin therapy [7]. In our case, the patient did not receive low-molecular-weight heparin therapy at the time of disease. The condition mostly affected middle-aged women between 55 and 65, which was also our case [9, 10]. One patient suffered a breast necrosis after a rectal cancer surgery, which corresponds with our patient's medical history [1, 5]. Paraneoplastic syndrome occurs in approximately 10% in cancer patients. But skin necrosis has not been described as complication of paraneoplastic syndromes [11]. In most of the cases described the patients were also obese, unlike our patient. Chen et al. published new findings in their paper about the role of proteins C and S and the role of Antithrombin III in the coagulation process, stating that these findings would enhance our understanding of the mechanisms leading to the condition. The authors also claimed hypercoagulable states following the introduction of anticoagulant therapy were a major factor contributing to the condition [12, 13]. A number of possible causes have been proposed as leading to breast necrosis, such as trauma, previous treatment with anticoagulant therapy, specific vitamin deficiencies, etc. [9]. However, despite the efforts of medical researchers and workers to understand the etiopathogenesis of this condition, its causes remain unclear; it is known for sure that a range of factors contribute to its development. The fact that the condition is very rare explains why relatively little attention is paid to identifying its causes [1, 5, 7]. Surgery was the preferred medical treatment in almost all of the cases described. In some of these cases the operative procedure was done in two stages, as was the case with our patient [14, 15].

The incidence of breast necrosis caused by anticoagulant therapy is very low, and when such patients are admitted to hospital, breast inflammation are initially suspected. The information about the sudden development of the condition indicates that it might be acute,

and the clinical description that it might be an emergency requiring immediate treatment. Timely diagnosis is essential for reducing morbidity. Another important piece of information concerns previous anticoagulant therapy administration, as it may help the physician suspect breast necrosis. In the majority of cases described in medical literature, the condition progressed very fast, leading to a clearly demarcated area of necrotic tissue, which made the physicians opt for necrectomy rather than needle biopsy of the breast.

#### NOTE

The case was presented in the form of poster presentation at the 2nd Congress of Pathologists in Bosnia and Herzegovina with International Participation, which was held in Banja Luka, May 10–12, 2012. The abstract titled “Haemorrhagic infarction with skin necrosis of the breast complicating anticoagulant therapy” is printed in the Abstract Book. The article was not published or sent to other medical journals for publishing.

This case report was approved by the institutional ethics committee, and written consent was obtained from the patient for the publication of this case report and any accompanying images.

**Conflict of interest:** None declared.

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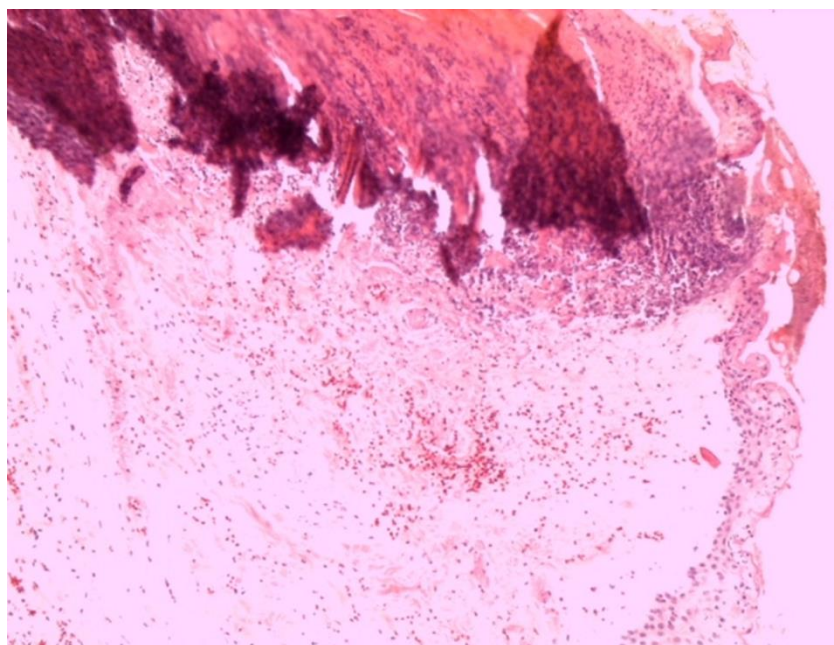


**Figure 1.** Breast necrosis upon admission

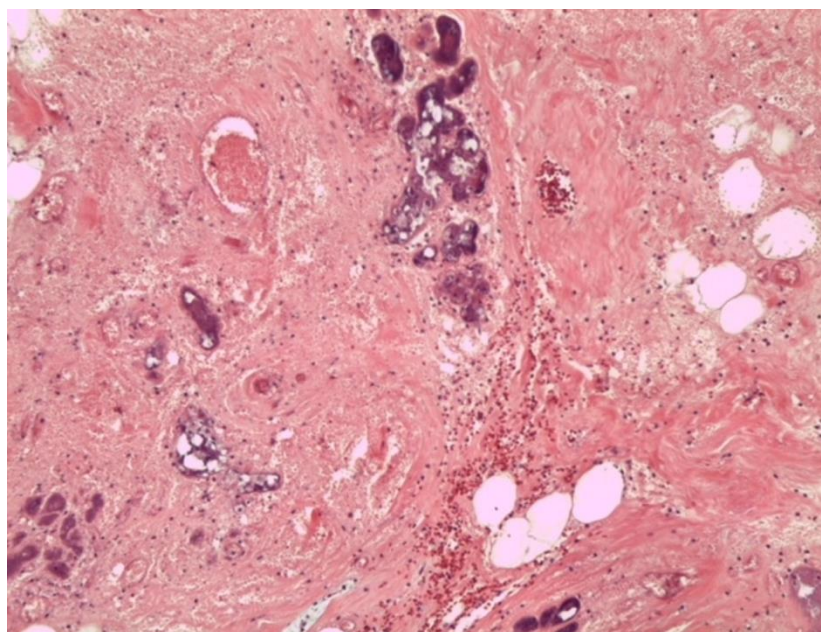




**Figure 2.** Breast necrosis with demarcation line, second day upon admission

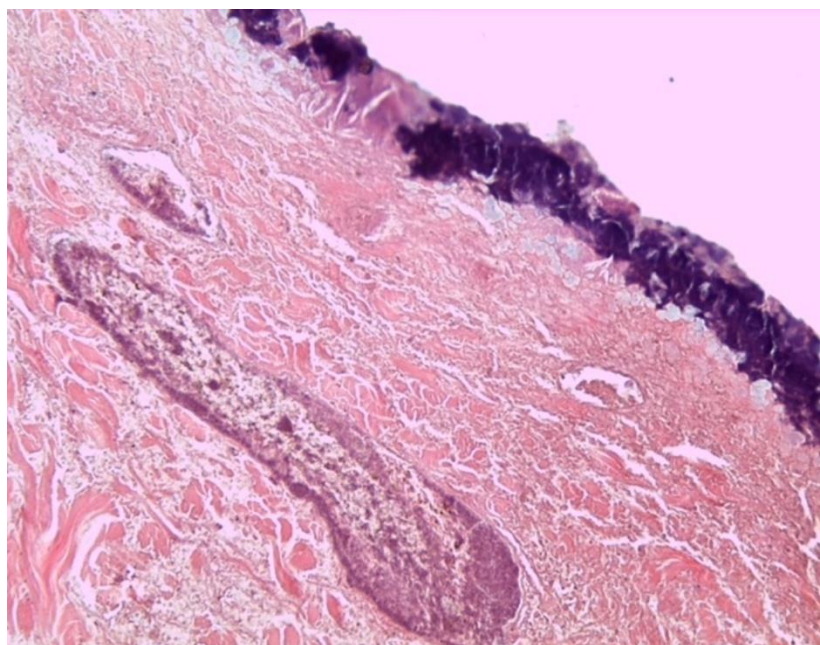


**Figure 3.** A loss of cellular details in breast tissue (H&E, 20×)



**Figure 4.** Necrosis areas of the breast parenchyma (H&E, 20×)





**Figure 5.** Inflammatory changes within and surrounding of small arteries (H&E, 20×)