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Interplay between acute coronary syndromes and cancer: insights into pathophysiology, diagnostic challenges, and treatment options

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Abstract

Acute coronary syndromes (ACS) and cancer are among the leading causes of death worldwide. In recent years, increasing evidence has suggested an interplay between these 2 conditions. This article reviews the pathophysiology, diagnostic challenges, and treatment options for ACS and cancer. The interplay between these conditions may be due to environmental, genetic, and metabolic factors. For example, smoking, hypertension, and obesity are risk factors for both ACS and cancer. Diagnosis of ACS and cancer can be challenging because the symptoms of these conditions often overlap. For example, chest pain can be a symptom of both ACS and a neoplasms. Treatment options for ACS and cancer are varied and depend on the type of disease, stage of disease, and individual patient factors. Treatment for ACS may include angioplasty, stenting, or medication therapy. Treatment for cancer may include surgical removal of the tumour, radiation therapy, or chemotherapy.

Key words: acute coronary syndrome, cancer, pathophysiology, diagnosis, treatment.

Introduction

Cardiovascular diseases (CVD) and tumours stand out as primary causes of death not only in Poland but also around the world. Relying on data from Poland's Central Statistical Office (GUS) and the World Health Organization, it is evident that cardiovascular-related deaths account for nearly 180,000 fatalities in Poland each year [1]. Globally, this number rises to an alarming 17.9 million based on 2019 figures [2], meaning a third of all global deaths are from these causes. Such numbers stem from a combination of risk factors: from high cholesterol and hypertension to diabetes, smoking habits, and obesity. These disorders include conditions such as acute and chronic coronary syndromes, as well as heart failure.

Cancer diseases are the second most common cause of death, accounting for over a quarter of cases [3]. Their complex biology means that despite intensive research in oncology, and advancements in diagnosis and treatment, they remain a significant challenge for clinicians and researchers. Thanks to the tremendous progress made in oncology over the past several decades, which includes a better understanding of mecha-

nisms and applied treatments, the perception of cancer has shifted. Even though sometimes we are not able to cure cancers, the treatments used today make these diseases somewhat chronic in nature. This trend change is so significant that the current 5-year survival rate for certain cancers is higher than for chronic heart failure [4]. The continuous advancement in cancer treatment and the extension of patients' lives mean that clinicians must deal with the complications of these therapies. Many oncological drugs cause damage to the heart muscle even years after the cessation of chemotherapy. The coexistence of cardiovascular diseases and cancers is becoming a more frequent phenomenon in everyday medical practice. Beyond the association of cardiotoxic oncological treatments, there are many mechanisms causing interactions between cardiovascular diseases and cancers. Current research suggests that cardiovascular diseases and cancers might share a common biological and pathophysiological basis, related to inflammatory processes, endothelial dysfunction, and immune response. These shared mechanisms, combined with exposure, environmental, and genetic factors, may contribute to the development of both disease groups.

Having 2 potentially fatal diseases poses challenges in both diagnosing and treating them. The coexistence of acute coronary syndromes (ACS) and tumours presents a particularly intriguing and complex issue. ACS, with its rapid and often unpredictable course, can be a diagnostic and therapeutic challenge in the presence of cancer diseases. It turns out that both ACS and cancers have a multitude of shared risk factors. This article attempts to organize and summarize the knowledge we currently have on this topic.

Pathophysiological basis of ACS in cancer patients

ACS are medical conditions characterized by a rapid reduction in coronary blood flow. The most frequent cause of this is a clot formed on a ruptured atherosclerotic plaque, leading to either complete or near-complete vessel blockage. This in turn restricts blood flow, resulting in ischaemia of the heart muscle. In such instances, coronary angiography often reveals the artery causing the infarct, which is typically treated with angioplasty and frequently stent placement [5]. For cancer patients, the pathophysiology of ACS has some distinctions. Some studies have demonstrated that in patients undergoing treatment with checkpoint inhibitors (ICI), vascular changes progress more quickly [6, 7]. Moreover, many cancer patients often do not exhibit any symptoms of coronary disease [8]. Among the potential mechanisms that might lead to ACS in these patients are the inflammatory conditions accompanying cancer and the activation by the tumour of pro-coagulant pathways in the body. Additionally, numerous studies have highlighted shared risk factors for cardiovascular diseases, including heart attacks, and cancers.

It has been demonstrated that one common denominator between cardiovascular diseases and cancers is a genetic basis [9]. Gene polymorphisms represent varying sequences of specific genes found in the population, which can lead to structural differences in proteins and, consequently, functional disparities [10]. From an epidemiological standpoint, these variations can either enhance susceptibility to diseases or offer protective effects. A case in point regarding the significance of gene polymorphisms in cancers involves certain variants linked to DNA repair capabilities. These polymorphisms may induce alterations in the structure or expression of proteins accountable for repairing DNA damage, influencing a cell's ability to detect and fix these damages. One instance where polymorphisms impact both the cardiovascular system and cancer diseases is the polymorphism in the BRCA 1/2 gene. Improperly repaired DNA due to defective BRCA proteins can lead to premature cellular aging, especially in metabolically stressed tissues like the cardiac muscle. Such premature aging can result in cardiomyocyte dysfunction, amplifying the risk of cardiovascular diseases. Furthermore, BRCA 1/2 are involved in down-regulating reactive oxygen species (ROS) and are associated with the levels of insulin-like growth factor-1 (IGF-1). Both extremely high and low IGF-1 levels lead to insulin resistance, which is a risk factor for CVD [11, 12].

Many data on the common genetic basis of cardiovascular diseases and cancers have been provided by genome-wide association studies (GWAS), which have described many thousands of single-nucleotide polymorphisms (SNPs). Studies indicate common pathways leading to disease [13]. For example, tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine that is responsible for many processes (involved in modulating immunity, inflammation, apoptosis, and cell proliferation), is involved in promoting carcinogenesis, angiogenesis, and metastasis. On the other hand, many pro-inflammatory cytokines, including TNF-α, are involved in the process of atherosclerotic plaque formation. Other studies show increased levels of interleukins (IL-6, IL-1β) in both groups of patients. The Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) showed that reducing inflammation can have a beneficial effect on the treatment of cardiovascular diseases. In this study, patients who had a heart attack and an elevated C-reactive protein (CRP) level ($\geq$ 2 mg/l) were giv-

en canakinumab (a specific antibody against IL-β). Treatment with this drug resulted in a reduction in the risk of further major cardiovascular events compared to the placebo group. In addition, other analyses have shown that canakinumab can reduce the risk of cancer [14].

Environmental factors have long been recognized as key determinants of the risk of developing cancers and cardiovascular diseases. One of the most significant and widely recognized risk factors is tobacco smoking. It is also the main risk factor for cardiovascular diseases, such as atherosclerosis or ischaemic heart disease [15]. Its harmful influence results from many mechanisms. One of them is the impairment of endothelial vessel function. It has been proven that tobacco smoke causes impaired vasodilation and is one of the factors initiating the formation of atherosclerotic plaque. Moreover, it induces an inflammatory state – studies have proven an increase in the number of leukocytes in the blood and elevated levels of IL-6 and CRP [16, 17]. Other studies indicate a connection between tobacco smoke and an increased tendency to form clots. This is due to platelet dysfunction and adverse changes in the concentrations of prothrombotic, antithrombotic, and fibrinolytic factors [18].

Nicotine addiction contributes to an increase in oxidative stress, leading to further damage to the endothelium of vessels and intensifying the process of atherosclerotic plaque formation. Studies also indicate a relationship between tobacco smoke and changes in the lipid profile in smokers. Although the exact mechanisms are not fully understood, it has been found that after quitting smoking, there is an improvement in the lipid profile, in the form of an increase in HDL levels [19]. Another known mechanism of the effect of nicotine addiction on the cardiovascular system is the increase in blood pressure, through the stimulation of the adrenergic system, which is an independent risk factor for developing cardiovascular diseases, including myocardial infarction [20]. On the other hand, smoking is directly related to many types of cancers, including lung cancer.

Overweight and obesity, defined based on body mass index (BMI), represent a global health issue and are increasingly common in developed societies. The health consequences associated with excessive body weight are numerous and affect various systems and organs. Obesity is considered one of the key modifiable risk factors for many types of cancer. Mechanisms linking obesity to cancer risk include chronic inflammation, hormonal imbalances, and insulin resistance [21]. For instance, a high level of oestrogens, often observed in obese women, can contribute to an increased risk of breast cancer [22]. Similarly, chronic inflammatory states present in obese individuals can promote carcinogenesis, leading to an elevated risk of colorectal and pancreatic cancers. Obesity, being an inflammatory and metabolic condition, also significantly impacts the cardiovascular system. Visceral fat, characteristic of abdominal obesity, appears to be particularly harmful, releasing a range of pro-inflammatory cytokines, such as TNF-α and IL-6, which contribute to vascular endothelial damage. Furthermore, obesity often goes hand in hand with insulin resistance, leading to metabolic disorders like type 2 diabetes, which is a strong risk factor for cardiovascular diseases. Moreover, overweight and obesity are directly linked to elevated blood pressure, dyslipidaemia, and increased mechanical strain on the heart, accelerating atherosclerotic processes.

Both the presence of cancer itself and oncological treatment have consequences on the functioning of the cardiovascular system. In the context of acute coronary syndromes, it is important to focus on vascular toxicity induced by oncological therapy. In clinical practice, 2 main models of vasotoxicity can be pointed out: irreversible (type 1) and reversible (type 2). The former causes permanent changes in arteries, while the latter is associated with temporary arterial constriction induced by the drug [23].

The pathophysiology indicates 3 main types of vascular toxicity: A, B, and C. Type A appears after the use of BCR-ABL kinase inhibitors, with ponatinib, a newest generation drug, showing the highest level of toxicity. In type B, the predominant role is played by clot formation under the influence of oncological treatment, with cisplatin and VEGF inhibitors leading the way. The latter inhibits angiogenesis in tumours but also negatively affects healthy vessels. Angiogenesis inhibitors often lead to hypertension, which results from the disruption of arterial cell function.

Type C toxicity, often associated with drugs like 5-fluorouracil or capecitabine, results in coronary artery constriction. Symptoms such as angina pain typically appear shortly after drug administration. In response, patients are often discontinued from further treatment with these drugs [8].

Types of myocardial infarction in cancer patients and diagnostic differences

From an electrocardiographic perspective, acute coronary syndromes can be divided into infarctions with ST-T segment elevation and without ST-T segment elevation. STEMI ACS is most often caused by a complete closure of the coronary artery by a clot. As previously mentioned, the primary cause of this condition is attributed to a rupture or erosion of the atherosclerotic plaque [5]. From a clinical classification perspective, we define it as

a type 1 heart attack. In oncological patients, however, acute coronary syndrome without ST-T segment elevation is more common, in which there is a residual flow in the artery responsible for the infarction and where collateral circulation is relatively well developed [23]. Considering the clinical classification in this group, a type 2 heart attack is more common, in which myocardial ischaemia occurs due to insufficient oxygen supply to the heart muscle cells. The presence of a tumour in the body causes inflammation in the body, and additionally, tumour cells produce certain prothrombotic factors. Within 6 months of the oncological diagnosis the risk of an acute coronary syndrome is significantly higher (2-fold higher than in the general population) [24]. In combination with the applied oncological treatment, all these factors lead to destabilization of the atherosclerotic plaque and limited coronary flow.

There are also differences in terms of clinical presentation. In the population of patients without cancer, chest pains, including anginal pains, are the most common clinical presentation of acute coronary syndrome, while in the case of cancer patients, in as much as 44% of patients, shortness of breath dominates. Less than 1/3 experience chest pain, and about 20% experience hypotension [23, 25]. This may be due to polyneuropathy after chest radiotherapy. It is also significant that oncological patients often use strong pain relief due to painful symptoms in the course of cancer.

Differences in the pathomechanism of acute coronary syndrome should prompt clinicians to be cautious when making a decision regarding coronary angiography in these patients. One should always carefully trace the course of the existing cancer, the treatment being used currently and in the past, laboratory test results, the patient's haemodynamic status, comorbidities, and the patient's further prognosis. The diagnosis is also complicated by the fact that troponin levels in oncological patients are often elevated. This may be due to continuous and consistent damage to the heart muscle over time as a result of cancer and its treatment. There is no clear guidance in the available literature regarding the management of coexisting cancer and acute coronary syndromes. In the context of the ACS diagnosis itself, one should proceed in accordance with current guidelines. However, in order not to expose cancer patients to unnecessary and invasive coronary angiography, which carries a risk of complications, in the absence of ST-T segment elevation and the presence of positive troponin, a characteristic increase in troponin indicative of ACS should be demonstrated. If troponin values do not show a dynamic increase, a conservative strategy seems to be better for patients.

Treatment strategies for acute coronary syndrome in oncology patients

According to the ESC guidelines, in the case of a STEMI-type heart attack, percutaneous coronary angioplasty is always the preferred treatment method. For NSTEMI ACS and type 2 heart attack, reversible causes of ischaemia (e.g. anaemia) should be considered first, followed by consideration of invasive treatment. There are still insufficient data on the results of percutaneous treatment of STEMI in oncology patients. From the conducted analyses, it is clear that patients with STEMI and cancer were less often subjected to PCI compared to patients without tumours [26]. Furthermore, it was shown that in patients with STEMI ACS and cancer, drug-eluting stents (DES) and glycoprotein IIb/IIIa inhibitors were less frequently used. Additionally, they had a higher overall mortality in a one-year observation compared to patients without tumours [26, 27]. It seems that this may partly result from a smaller percentage of invasive treatment. The choice of an invasive strategy in patients with ACS and cancer should always be carefully considered. Radial artery access is preferred. This is associated with fewer complications, and in case of necessity, a precise point compression can be applied, so that achieving haemostasis is possible even in patients with thrombocytopaenia [28]. The femoral artery access can also be considered, but it carries a higher risk of bleeding, especially in the case of puncture above the inguinal ligament. In such a case, retroperitoneal bleeding may occur, which is potentially impossible to control, especially in the context of cancer, accompanying thrombocytopaenia, and the pharmacological treatment used during the intervention (antiplatelet and anticoagulant therapy) [28–30].

The choice of implanted stent is not a simple issue. Current guidelines no longer recommend the implantation of bare-metal stents (BMS), in favour of DES. As stents are foreign bodies, blood platelets upon contact with their surface can form a clot and lead to stent thrombosis. For this reason, dual antiplatelet therapy (DAPT) is recommended. As mentioned earlier, oncology patients often face the problem of thrombocytopaenia, which results in an increased risk of bleeding. For this reason, using third-generation DES, which allow for a shorter DAPT duration, seems to be the best approach for these patients. As an alternative procedure, if technical and anatomical conditions allow, balloon angioplasty (POBA) should be considered. Its great advantage is the short duration of DAPT (it is recommended that DAPT be used for at least 2 weeks), after which cancer treatment can be resumed (optimally after 4 weeks) [30]. For these reasons, balloon angioplasty appears to be

particularly attractive for patients requiring onco-surgery.

In the context of the safety of performing coronary angiography in patients with thrombocytopaenia, it seems to be safe if the platelet level is > 10,000 per microlitre. At this platelet level, prolonged use of acetylsalicylic acid is also safe. If the platelet level is between 10,000 and 30,000 per microlitre, balloon angioplasty with the DAPT duration described above is probably the most appropriate procedure. In cases where platelet counts are > 30,000 per microlitre, PCI with DES stent implantation can be considered. According to guidelines, the optimal duration of DAPT after DES stent implantation is at least 12 months, but with the latest generation stents, this duration can be reduced.

One of the revascularization treatment options for patients with ACS is coronary artery bypass grafting (CABG). It can be safely performed when the platelet count is > 50,000 per microlitre. A clear advantage of this method is that there is no need for DAPT in this case. On the other hand, for oncology patients who have undergone radiotherapy in the chest area, technical difficulties may arise during surgery due to radiation-induced changes in the mediastinum and chest vessels [31].

Pharmacological treatment

The choice of pharmacological treatment in oncology patients should also be approached with caution. Although clear guidelines exist for the pharmacological treatment of patients with myocardial infarction and heart failure, there is once again a lack of clear data regarding the same issue in the context of oncology patients. It seems that the risk of bleeding in them is so significant that thrombolytic therapy should not be used in this group.

DAPT in oncology patients should be based on the use of acetylsalicylic acid (in patients with a platelet count > 50,000 per microlitre), and its second component should primarily consider clopidogrel, as the drug with the lowest percentage of haemorrhagic complications compared to prasugrel and ticagrelor. In a study conducted by Iliescu *et al.* it was shown that in patients treated with PCI with stent implantation and subsequent dual antiplatelet therapy with acetylsalicylic acid and clopidogrel, there was no increased risk of bleeding [32]. Of course, further studies should be conducted to precisely determine the benefits and risks of using DAPT. The use of glycoprotein IIb/IIIa inhibitors can also be considered because their half-life is short, and in the case of bleeding symptoms it is possible to quickly discontinue the drugs and subsequently stop their action.

One should be aware of the interaction of chronically administered oncological treatment with cardiological drugs. Some drugs are metabolized by the same liver enzymes, so their simultaneous use can lead to undesirable interactions. For example, both paclitaxel and simvastatin are metabolized by the cytochrome CYP2C8, consequently reducing the bioavailability of the statin. Recently, attention has also been drawn to the potential positive benefits of statins on tumours. The pleiotropic effects of this group of drugs are well-known. One of these effects is anti-inflammatory and anti-angiogenic action, which can have a beneficial effect on inhibiting tumour formation [33].

Regarding other drugs used in ACS, the approach to patients with cancer should not be different. It is necessary to include β-blockers, ACE-I, and MRA if needed. It has been proven that such treatment has cardioprotective effects and may affect the extension of patients' lives [34, 35].

Summary

Acute coronary syndromes in oncological patients pose a particular challenge for clinicians. In these patients, one should be aware of a somewhat different clinical presentation. The most common symptom reported by these patients is dyspnoea, while in patients without cancer, it is chest pain. Moreover, in these patients, NSTEMI-type heart attacks and type 2 heart attacks are more common. One should carefully weigh all the pros and cons when deciding on invasive treatment. Oncological patients often present with thrombocytopaenia, so the risk of bleeding both during the procedure and during the use of DAPT is higher than in patients without cancer.

In conclusion, the topic is very complex, and the choice of appropriate therapy should be made individually.

Conflict of interest

The authors declare no conflict of interest.

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