Case report

Acute coronary syndromes in oncology: conservative or invasive strategies? Case study and literature review

Michał Wilk[1,2], Anna Walaszkowska-Czyż[2], Arkadiusz Rak[3], Michał Piłka[1], Sebastian Szmit[1]

[1] Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Centre of Postgraduate Medical Education, European Health Centre, Otwock
[2] Department of Clinical Oncology, European Health Centre, Otwock
[3] Cardiology Centre, Józefów

Correspondence:
Michał Wilk
Department of Pulmonary Circulation, Thromboembolic Diseases and Cardiology, Centre of Postgraduate Medical Education, European Health Centre, Otwock
ul. Borowa 14/18, 05-400 Otwock
e-mail: wilk.m@onet.eu

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ABSTRACT

We present the case of a 70-year-old male patient with metastatic and castration-resistant prostate cancer as well as advanced bladder cancer, who suffered a non-ST-elevation myocardial infarction (NSTEMI). The cause of ischemia was critical left main stem stenosis, and right coronary artery stenosis. Initially, the patient was qualified for conservative treatment, but due to the intensifying symptoms of myocardial ischemia, it was decided that a hemodynamic intervention was necessary. Two drug-eluting stents were implanted, leading to clinical improvement. Following the treatment, the patient was considered as a candidate for further anti-cancer therapy. Unfortunately, due to the bladder cancer progression, anaemia and haemorrhage, his clinical condition exacerbated, and the patient died about 1 month from the cardiac intervention. Apart from the case description, the paper includes a review of literature on the treatment of acute coronary syndromes without ST-segment elevation in cancer patients.

Key words: cancer, acute coronary syndrome without ST-elevation, antiplatelet therapy

INTRODUCTION

An acute coronary syndrome (ACS) is one of the causes of premature deaths in the general population. In cancer patients, increased "thrombotic readiness" and the anti-cancer treatment involved may further increase the risk of ACS. There have been no detailed prospective studies into the effectiveness of both invasive and conservative treatment in that population of patients, but we do know that it is a group of patients that requires a case-by-case approach, especially in the case of elderly patients. Thus, careful consideration is recommended, when assessing the risks and benefits associated with different treatment methods.

CASE DESCRIPTION

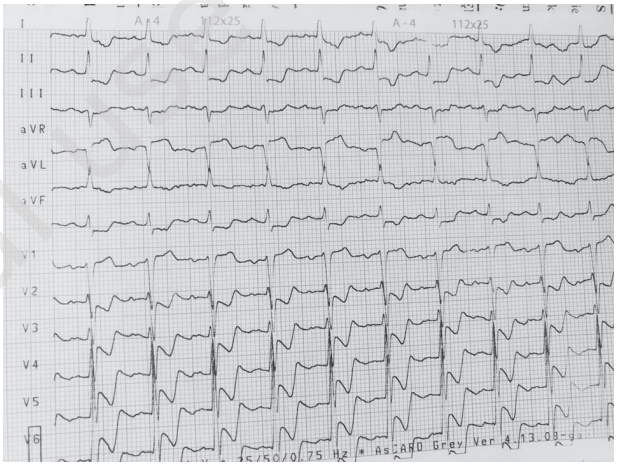
In April 2017, a 70-year-old male patient was admitted to the Department of Oncology, European Health Centre, Otwock, diagnosed with advanced prostate cancer with bone metastases, treated with abiraterone acetate, and with advanced bladder cancer. The reasons for hospitalization included his poorer general condition, fatigue, and lower exercise tolerance with dyspnoea after walking several dozen metres. His lab test results revealed anaemia with Hgb 7.9 g/dl, leukopenia 2.9 thou/µl, and an upper limit level of creatinine 1.21 mg/dl.

The patient's history revealed a Gleason 9 (5 + 4) prostate cancer, diagnosed in 2007, and initially treated with leuprorelin acetate (a-LHRH). Urinary bladder cancer was detected in 2015, with histologic examination confirming the diagnosis of carcinoma urotheliale G3, pT4, N1 (abdominal CT revealed pathological iliac lymph nodes). In the period of April–September 2015, the patient received 6 courses of palliative chemotherapy, involving the docetaxel 70 mg/m^2 + cisplatin 70 mg/m^2 regimen, followed by stabilization of both tumours. In June 2016, due to the confirmed progression of bone and bladder lesions, he underwent a second-line chemotherapy with the use of cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2. In March 2017, the patient was qualified for the National Health Fund reimbursement programme in the treatment of prostate cancer with abiraterone acetate, as his PSA level had been increasing rapidly. On the other hand, the imaging tests performed revealed stabilization of the urinary bladder cancer. The patient's internal medicine history included a long-standing arterial hypertension (treated with ACE-inhibitors and β-blockers) and hypercholesterolemia (treated with atorvastatin).

Upon admission, the patient's general condition was average, his arterial pressure was 110/60 mmHg, cardiac function was regular 90/min, and saturation was normal at the level of 96%. The patient did not complain about chest pain, syncope or palpitation. Physical examination revealed bilateral basal crepitations over lung fields, and oedema of the distal ⅓ of lower legs.

As part of further diagnostics, a 12-lead resting ECG was performed, revealing regular sinus rhythm ca. 110/min, and ST-T depression in leads I, II, III, aVF, V_2–V_6 (fig. 1).

FIGURE 1.
12-lead ECG – visible ST-T depression in leads I, II, III, aVF, V_2–V_6.



Laboratory test results revealed a baseline troponin level of 0.71 ng/ml (normal range < 0,14). One hour later, the level was slightly higher, amounting to 0.732 ng/ml. NT-proBNP concentration was 12 711 pg/ml.

Having taken into consideration the overall clinical picture and results of the additional tests, a non-ST-elevation myocardial infarction was diagnosed. The risk of in-hospital death was estimated as high (GRACE score 158). The risk of haemorrhage was also assessed as high (CRUSADE score 47). The patient was informed about the diagnosis and the possible management strategies. In light of the coexisting 2 advanced tumour types, significant risk of bleeding (presence of urinary bladder tumour), and lack of chest pain, the patient did not consent to invasive treatment. Hence, a conservative strategy was applied, involving 300 mg of acetylsalicylic acid (ASA) and 5000 units SC of dalteparin, alongside the continued prior treatment with an ACE-inhibitor, β-blocker and statin.

Unfortunately, in follow-up tests, increased troponin levels were observed, reaching 1.07 ng/ml 6 hours later. Additionally, parasternal chest pain set in at the time, radiating to the left upper extremity and the mandible. Due to the progression of myocardial ischemia and the sternocardiac pain, the patient consented to an invasive procedure.

He was transferred to the cath lab of the Cardiology Centre in Józefów, where urgent coronary angiography was performed. The examination revealed critical left main stenosis as well as right coronary artery stenosis (fig. 2a and 3a). Echocardiography revealed new areas of hypokinesis of the apex, apical and medial segment of anterior wall, and of the interventricular septum. Ejection fraction was 54%.

FIGURE 2a.
Critical stenosis of the left main coronary artery (arrow).

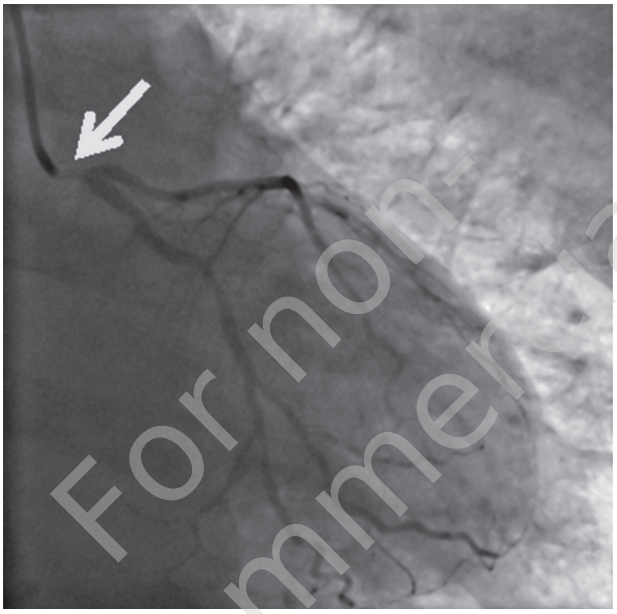


FIGURE 2b.
Normal flow through the left main coronary artery.

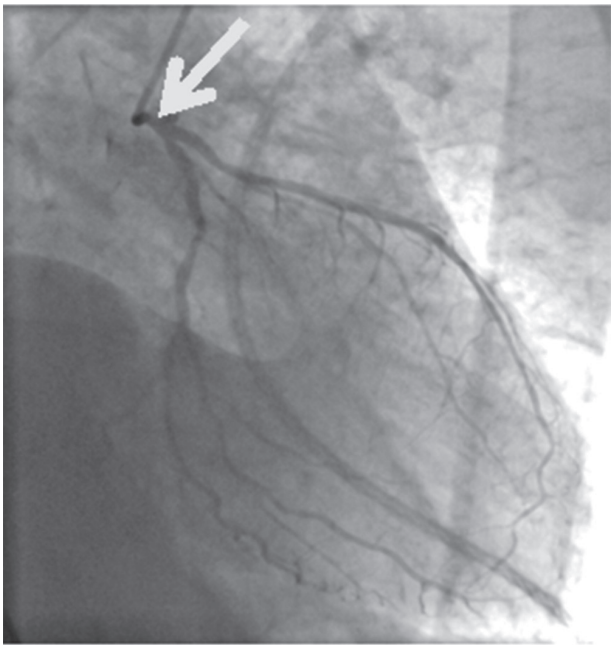


FIGURE 3a.
Segmental stenosis of the right coronary artery (arrow).

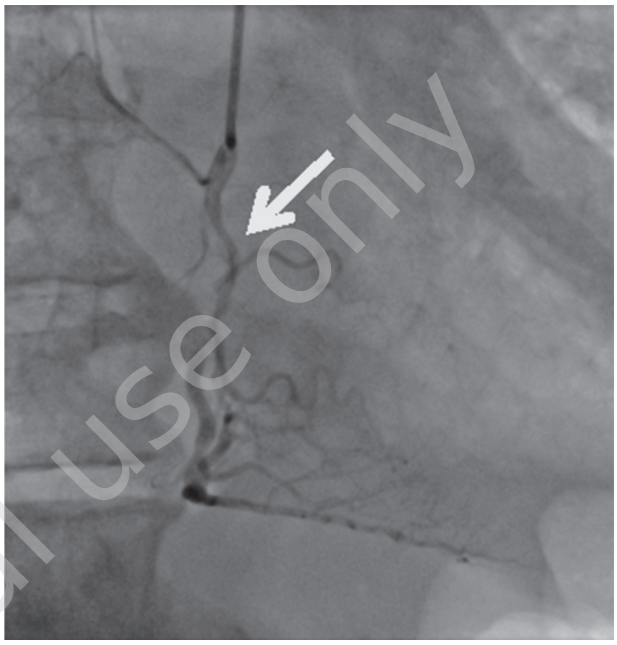
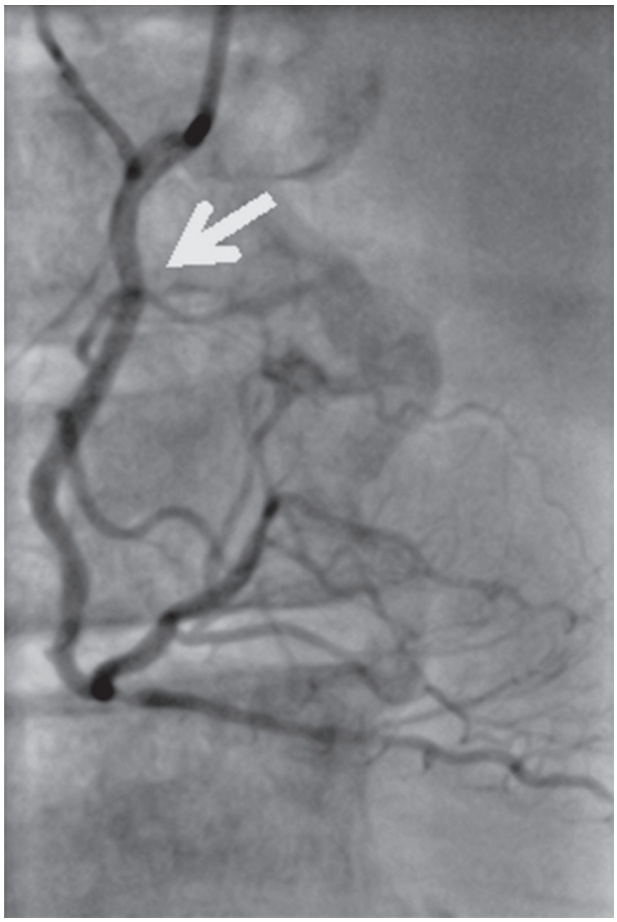


FIGURE 3b.
Normal blood flow through the right coronary artery (arrow).



Coronary angioplasty with implantation of 2 drug-eluting stents (DES) was performed, leading to a significant improvement in the coronary circulation (fig. 2b and 3b). The patient was instructed on using a dual anti-platelet therapy (ASA + clopidogrel) for a 12-month period, and he was discharged from hospital in a stable general condition.

One month from the cardiac intervention, the patient reported to the oncology clinic in order to continue his prostate cancer treatment with abiraterone acetate. At that time, the patient assessed his health condition as good, and did not report any alarming symptoms. He did not complain about chest pain, syncope, palpitation or lower extremity oedema. With a view to a possible resumption of the prostate cancer treatment, the patient was referred for non-invasive cardiovascular diagnostics aimed at assessing his cardiac efficiency, coronary reserve and potential hemodynamic and electrocardiography abnormalities. Unfortunately, several days later, the patient suffered a massive urinary tract bleeding, and was admitted to a local hospital, where he died a few days later of bladder cancer progression.

DISCUSSION

Patients with a diagnosed advanced neoplastic disease and acute coronary syndrome constitute a great diagnostic and therapeutic challenge. There are indeed no accurate guidelines on how to manage that group of patients. Thus, decisions on the choice of strategy, invasive treatment method and adequate pharmacotherapy are very difficult and often require a tight collaboration of oncology and cardiology specialists.

The above presented case involves a patient with a long history of cancer, 2 advanced neoplastic processes, several lines of palliative treatment, anaemia, and related acute coronary syndrome without ST-segment elevation. It is estimated that around 2% of patients on cisplatin may develop thromboembolic complications [1].

In accordance with the 2015 guidelines of the European Society of Cardiology (ESC) on the management of acute coronary syndromes, one should determine the level of cardiac troponins as quickly as possible in the case of ECG abnormalities that are indicative of myocardial ischemia. If high-sensitivity tests are available, it is recommended that a rapid rule-out protocol be applied within 0 h/1 h, and should the test result be inconclusive, another test should be performed 3–6 hours later [2]. In the case discussed above, the 2 values were very similar, and only the next measurement, performed 6 hours later, was significantly higher than the baseline result.

At the time of diagnosis of an NSTEMI heart attack, prognosis is typically assessed, with the use of the commonly available scores, including the GRACE score for the assessment of ACS-related risk of death [3], and the CRUSADE bleeding risk calculator [4]. Results of the patient in question indicated a high risk of in-hospital death and bleeding. Unfortunately, the scores do not take malignancies into consideration as one of the possible reasons behind poorer patient prognosis.

Selection of a therapeutic strategy (conservative or invasive) is an essential element of the management of advanced cancer with concurrent acute coronary syndrome. Table 1 lists all the factors

TABLE 1.
Risk criteria indicative of the superiority of invasive strategy in non-ST-elevation acute coronary syndrome (NSTEMI), based on the 2015 ESC guidelines on the management of NSTEMI [2].

Group	Characteristic	Management
Very high risk	• unstable hemodynamic condition or cardiogenic shock • recurrent or persisting chest pain resistant to conservative therapy • life-threatening arrhythmia or cardiac arrest • mechanical MI complications • acute heart failure • recurrent dynamic ST-T changes, especially with transient ST segment elevation	urgent invasive strategy < 2 h
High risk	• increase and decrease in the cardiac troponin levels, indicative of MI • dynamic ST or T wave changes (symptomatic or clinically silent) • GRACE score > 140	early invasive strategy < 24 h
Moderate risk	• diabetes • renal insufficiency (eGFR < 60 ml/min/1.73 m^2) • LVEF < 40% or congestive heart disease • early post-infarction angina • prior PCI • prior CABG • GRACE score 109–140	invasive strategy < 72 h
Low risk	• any of the above listed characteristics	non-invasive tests on a needs basis or optional invasive strategy < 72 h

which should be taken into consideration, when deciding on a revascularization procedure.

The above mentioned guidelines, however, do not take into account patients suffering from disseminated neoplastic processes or senior (geriatric) cancer patients, whose life expectancy is often as short as several months. Therefore, the question arises of whether one should always aim at an escalation of invasive treatment in that population of patients. In 2016, results of the first American analysis of invasive treatment outcomes in acute coronary syndromes in metastatic cancer patients were presented (2000–2009). The study, looking into in-hospital mortality, involved nearly 50 thousand subjects. The patients were divided into several groups depending on the ACS type (STEMI vs. NSTEMI) and the strategy applied (conservative vs. invasive treatment). The authors demonstrated that in the NSTEMI cases, results of the 2 strategies had been getting closer to one another since 2000, and reached an almost identical value in 2009. They linked it to ever better and more efficacious conservative treatment methods [5]. Another study looking into the impact of invasive cardiac treatment on long-term outcomes in ACS patients with disseminated malignancies was carried out by Yusuf et al. In their retrospective analysis, they reviewed patients discharged from the Texas MD Anderson Cancer Center with the diagnosis of acute coronary syndrome (n = 456). The authors observed no difference in overall survival irrespective of the ACS type (NSTEMI vs. STEMI). An univariate analysis demonstrated that poorer prognosis was associated with prior chest radiotherapy, chemotherapy, diagnosis of leukaemia or lymphoma, lack of ASA, β-blocker or statin treatment, and no invasive cardiovascular treatment. However, a multivariate model only indicated ASA and β-blocker use as factors that significantly reduced the risk of death (by 23% and 36%, respectively). A limitation of the study was a small number of patients who had received invasive treatment (n = 15), and a small number of patients on ASA (n = 7) [6].

Antiplatelet therapy in cancer patients is a yet another important issue. Patients with disseminated malignant diseases are exposed to frequent thrombocytopenic episodes, which is associated with more frequent haemorrhagic events. Initiation of ASA or another antiplatelet drug may therefore further increase the risk of a life-threatening haemorrhage. In 2007, Sarkiss et al. published the results of a small study, involving 70 patients with ACS and concurrent malignant tumour, divided into 2 groups depending on their platelet count (n = 43 for PLT > 100 thou, n = 27 for PLT ≤ 100 thou). The study looked into the rate of survival longer than 7 days from an acute coronary syndrome, and into the incidence of bleeding as a result of ASA therapy. The > 7-day survival rate was higher in patients with normal platelet counts (77% vs. 37%; p = 0.0012). Additionally, in both groups the survival rate was higher for those patients who were treated with ASA. Moreover, in the PLT < 100 thou study arm, the 7-day survival rate was 90% for those on ASA, and only 6% for patients who did not receive acetylsalicylic acid. Thus, treatment with acetylsalicylic acid was not found to be associated with life-threatening haemorrhages in either of the groups under analysis [7]. On the other hand, the patient described above experienced a massive bleeding, requiring RBC transfusion, over one month into the ASA therapy combined with clopidogrel.

The duration of antiplatelet treatment is also of great significance. So far, there have been no dedicated randomized clinical trials that would make it possible to determine an optimum duration of dual antiplatelet therapy (DAPT) in patients from the high bleeding risk groups. Based on the 2017 ESC guidelines, it is standard practice in the general population, irrespective of the adopted ACS management strategy, to administer ASA and P2Y12 inhibitor for 12 months, unless there are contraindications involved. If the risk of haemorrhagic complications is high, one should consider withdrawing the P2Y12 inhibitor after 6 months of DAPT in patients who have undergone a percutaneous coronary intervention (PCI). On the other hand, if ACS is managed conservatively, and the risk of bleeding is high, one should consider DAPT use for a minimum of one month [8]. Table 2 presents the management algorithm proposed by Binder and Luscher. They qualify a neoplastic disease as a high risk factor of haemorrhagic complications and recurrent myocardial ischemia [9].

TABLE 2.
Suggested duration of dual antiplatelet therapy, following drug-eluting stent implantation in stable coronary disease, depending on the individual risk profile, based on Binder and Luscher [9].

		Risk of ischemia		
		Low	Moderate	High
Risk of bleeding	Low	6 months	12 months	≥ 30 months
	Moderate	3–6 months	6–12 months	12 months
	High	≤ 3 months	3–6 months	6–12 months

The patient under discussion was on his third course of abiraterone acetate treatment, when he was diagnosed with ACS. The drug is a selective P450 c17 cytochrome (CYP17) inhibitor, i.e. an enzyme indispensable for the androgen biosynthesis in the testicles, adrenal glands, and prostate cancer cells. Cardiovascular complications related to its use include the development of arterial hypertension, hypokalaemia, peripheral oedema and cardiac rhythm abnormalities (atrial fibrillation, QT prolongation). The drug may also predispose patients to an exacerbation of coronary artery disease [10]. However, one should note that in

a phase III registration study, involving 1195 patients, comparing the efficacy and safety of abiraterone acetate + prednisone vs. placebo + prednisone, the rate of cardiovascular complications was similar in both groups, amounting to 13% and 11%, respectively [11]. In another large randomized clinical trial (n = 1088), the incidence of myocardial ischemia was 4% in the abiraterone + prednisone group, and 3% in the placebo + prednisone population [12]. As the above mentioned registration studies did not include patients with a history of ACS in the preceding 6 months, the summary of product characteristics includes a recommendation to practice caution, when using the medication in persons with a history of ischemic heart disease [10]. The stable condition of the above described patient, and absence of cardiovascular symptoms encouraged the physicians to decide in favour of continuing the prostate cancer treatment. Unfortunately, during the qualification process, bladder cancer progression was observed, eventually leading to the patient's death.

SUMMARY

Patients with a diagnosed advanced cancer and acute coronary syndrome constitute a significant diagnostic and therapeutic challenge. The difficulty lies in the lack of guidelines dedicated to that particular population of patients. In such situations, close collaboration of oncology and cardiology specialists is essential. When taking decisions on the management strategy and pharmacotherapy, one should also take into consideration the current clinical condition, expected survival, and patient preferences. That approach is the only one that ensures maximum benefits for our patients.

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Michał Wilk: concept of the paper, case description, elaboration of the discussion and conclusions;
Anna Walaszkowska-Czyż: analysis and interpretation of the oncological test results, contribution to the proofreading of the manuscript;
Arkadiusz Rak: selection and elaboration of the figures, analysis of the cardiac test results;
Michał Piłka: analysis of the cardiac test results, contribution to the proofreading of the manuscript;
Sebastian Szmit: concept of the paper, case description, interpretation of oncological and cardiac test results, elaboration of the conclusions, proofreading of the manuscript.
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