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OPIS PRZYPADKU
CASE REPORT

Cardiotoxicity of immunotherapy in lung cancer in light of new ESC guidelines

Kardiotoksyczność immunoterapii w raku płuca w świetle nowych wytycznych ESC

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ABSTRACT

There has been rapid development of anticancer therapies involving monoclonal antibodies targeting immune checkpoints of the immune response. One of them is pembrolizumab (the anti-programmed death receptor 1 ligand – anti-PD-1) used in the treatment of malignant melanoma, non-small cell lung cancer, or triple-negative breast cancer, among others. The case presented in this paper refers to a patient suffering from adenocarcinoma of the lung with multiple metastases and associated diseases. During immunotherapy with pembrolizumab, acute myocarditis was diagnosed. The clinical course of this case study specifically demonstrates how important, in the context of oncology patients treated with immunotherapy, the continuous evaluation and control are of the occurrence of adverse toxic effects associated with anticancer treatment. First of all, potential PD-1 inhibitor cardiotoxicity is rare in patients undergoing therapy with this drug, which significantly hinders accurate differential diagnosis in this direction. Second, this adverse effect, although relatively rare, is often fatal. The following case study describes how, with high doses of glucocorticosteroids, the effects of pembrolizumab-induced toxicity can be effectively muted.

KEYWORDS

pembrolizumab, immune inhibitors, acute myocarditis, cardiovascular toxicity

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STRESZCZENIE

Obserwuje się dynamiczny rozwój terapii przeciwnowotworowej z udziałem przeciwciał monoklonalnych ukierunkowanych na odpornościowe punkty kontroli odpowiedzi immunologicznej. Jednym z nich jest pembrolizumab (humanizowane przeciwciało skierowane przeciwko receptorowi programowanej śmierci komórki 1 – anty-PD-1), stosowany w leczeniu m.in. czerniaka złośliwego, niedrobnokomórkowego raka płuc czy potrójnie ujemnego raka piersi. Przedstawiony w niniejszej pracy przypadek kliniczny dotyczy pacjenta chorującego na raka gruczołowego płuca z licznymi przerzutami oraz chorobami towarzyszącymi. W trakcie immunoterapii pembrolizumabem rozpoznano ostre zapalenie mięśnia sercowego. Przebieg kliniczny tej choroby w sposób szczególny wskazuje na to, jak istotna u pacjentów onkologicznych leczonych immunoterapią jest ciągła ocena i kontrolowanie niepożądanych efektów toksycznych związanych z leczeniem przeciwnowotworowym. Po pierwsze, potencjalna kardiotoksyczność inhibitora PD-1 występuje rzadko u pacjentów poddanych terapii tym lekiem, co znacznie utrudnia precyzyjną diagnostykę różnicową w tym kierunku. Po drugie, ten niepożądany efekt, choć występuje stosunkowo rzadko, często jest śmiertelny. Opisany przypadek wskazuje, w jaki sposób za pomocą wysokich dawek glikokortykosteroidów można skutecznie wyciszać efekty toksyczności wywołanej przez pembrolizumab.

SŁOWA KLUCZOWE

pembrolizumab, inhibitory immunologiczne, ostre zapalenie mięśnia sercowego, toksyczność sercowo-naczyniowa

INTRODUCTION

In recent years, there has been a significant increase in cancer detection, and this trend is projected to continue in future decades [1,2]. Modern medicine is striving to find modern solutions – therapies that aim to both improve the quality of and prolong the life of the patient [3,4]. In the last decade, a breakthrough in cancer therapy has been the use of immunotherapy, especially in cases of poor response to chemotherapy and radiotherapy [4]. One of the drugs used as part of cancer immunotherapy is pembrolizumab, an immunoglobulin G subtype 4 (IgG4), monoclonal antibody, an inhibitor of the immune checkpoint protein promoting cell death (PD-1) [5]. In many types of cancer, including lung adenocarcinoma, there is increased expression of the programmed death ligand 1 (PD-L1), which, after binding to its specific PD-1 receptor on the surface of T lymphocytes suppresses the immune system, allowing the cancer to grow [6]. Taking pembrolizumab abolishes this adverse effect and allows the immune system to activate against cancer cells, but also other cells in the body [7]. The increased immune response can lead to a series of adverse effects [7,8,9,10]. The description of the medical case study presented below demonstrates the diagnostic and differential management, as well as decisions on the inclusion of appropriate treatment in a patient, who developed a rare complication of pembrolizumab treatment in the form of myocarditis.

CASE REPORT

A 69-year-old patient burdened with multiple diseases – right lung adenocarcinoma, bronchial asthma, persistent atrial fibrillation, hyperlipidemia, urolithiasis, left kidney cysts, gallbladder stones and a history of central nervous system ischemic stroke, is the subject of the report.

In May 2022, the patient was diagnosed with adenocarcinoma of the right lung, with metastasis to lymph nodes – mediastinum, right hilum, visceral and retroperitoneal lymph nodes and to the skeleton. In the Katowice Oncology Center, the decision was made to start immunological treatment with pembrolizumab. The patient received the first infusion of immunotherapy on 06/07/2022. A dose of 2 mg/kg was used, and the cycle was repeated every 3 weeks. During the first week of pembrolizumab treatment, after the third cycle of administration, the patient reported symptoms in the form of pain in the neck and jaw area. The levels of myocardial necrosis markers were determined, noting their significant increase from the baseline values. In addition, during hospitalization in the Katowice Oncology Center, a positive result for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was obtained, with no respiratory symptoms. The patient was transferred for treatment, due to a significant increase in myocardial necrosis markers, to the 1st Department of Cardiology, Medical University of Silesia, Katowice. On physical examination, the patient's reported complaints of pain in the neck and jaw area lasting more than 1.5 weeks and a history of nicotinism were noteworthy. The patient denied complaints of a stenocardial nature. The family history was non-burdening.

Laboratory diagnostics were carried out during hospitalization, and transaminasemia, high lactate dehydrogenase, high values of myocardial necrosis markers and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) were detected (Table I).

Table I. Results of patient's laboratory tests on first day of hospitalization in Department of Cardiology; values exceeding accepted laboratory norms are marked in bold
Tabela I. Wyniki badań laboratoryjnych pacjenta podczas pierwszej doby hospitalizacji na oddziale kardiologii; wartości przekraczające przyjęte normy laboratoryjne są oznaczone pogrubionym fontem

Type of laboratory test	Reference value	Result
WBC	4.1–10.9 G/l	9.7 G/l
HB	13–18 g/dl	14.8 g/dl
PLT	150–400 K/ul	223 K/ul
ALT	35–40 U/l	**246 U/l**
AST	5–40 U/l	**275 U/l**
GGTP	< 40 U/l	**42.6 U/l**
FA	20–70 U/l	**53 U/l**
Bilirubin	0.2–1.1 mg/dl	0.71 mg/dl
Creatinine	< 1.2 mg/dl	0.93 mg/dl
CRP	< 5 mg/l	**9.5 mg/l**
LDH	120–240 U/l	**737 U/l**
D-dimers	500 ng/ml	388.83 ng/ml
Troponin T	0.009–0.070 ng/ml	**0.500 ng/ml**
CK-MB	< 25 U/l	**205 U/l**
NT-pro-BNP	68–112 pg/ml	**1724 pg/ml**

WBC – white blood cells; HB – hemoglobin; PLT – platelets; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGTP – gamma-glutamyl transpeptidase; FA – fatty acids; CRP – C-reactive protein; LDH – lactate dehydrogenase; CK-MB – creatine kinase myocardial band; NT-pro-BNP – N-terminal pro-B-type natriuretic peptide

A 12-lead electrocardiogram (ECG) revealed atrial fibrillation (AF), an intermediate heart axis, a maximum ventricular rate of about 100/min, and no myocardial ischemic changes (Figure 1). Transthoracic echocardiography (TTE) revealed a borderline left ventricular ejection fraction (LVEF) – 50%, no segmental left ventricular contractile dysfunction, and increased echogenicity of the left ventricle endocardium (Figure 2). A Holter ECG recorded AF, throughout the test period, with an average QRS complex rate of 68/min. It was decided to perform coronary angiography from the right radial access, with a contrast dose of 50 ml, visualizing small wall lesions of up to 10% in the left anterior interventricular branch of the left coronary artery and small wall lesions of up to 10% in the D1 branch. No lesions were visualized in the main trunk of the left coronary artery, the circumflex branch or the right coronary artery. Acute coronary syndrome was ruled out.

Looking for the cause of the significant increase in myocardial necrosis markers, accompanied by jaw and neck pain symptoms, cardiac magnetic resonance (CMR) was performed. Left ventricle basal segment oedema was visualized (Figure 3a). Using the late gadolinium enhancement (LGE) technique, intimal enhancement was visualized in basal segments of the left ventricle, with no visible coronary scarring, and normal pericardial plaques were imaged (Figure 3b, 3c). Taking into consideration the patient's medical history, medications used during oncology therapy, conducting differential diagnosis, a diagnosis of acute myocarditis in the left ventricular basal segments with preserved systolic function was made.

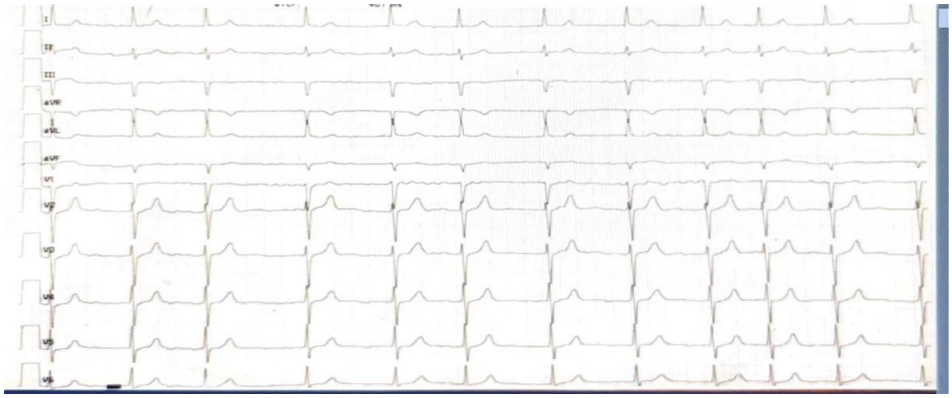

Fig. 1. 12-lead resting electrocardiogram (ECG) performed at beginning of patient's hospitalization in Department of Cardiology.
Ryc. 1. 12-odprowadzeniowe spoczynkowe badanie elektrokardiograficzne (EKG) wykonane na początku hospitalizacji pacjenta na oddziale kardiologii.

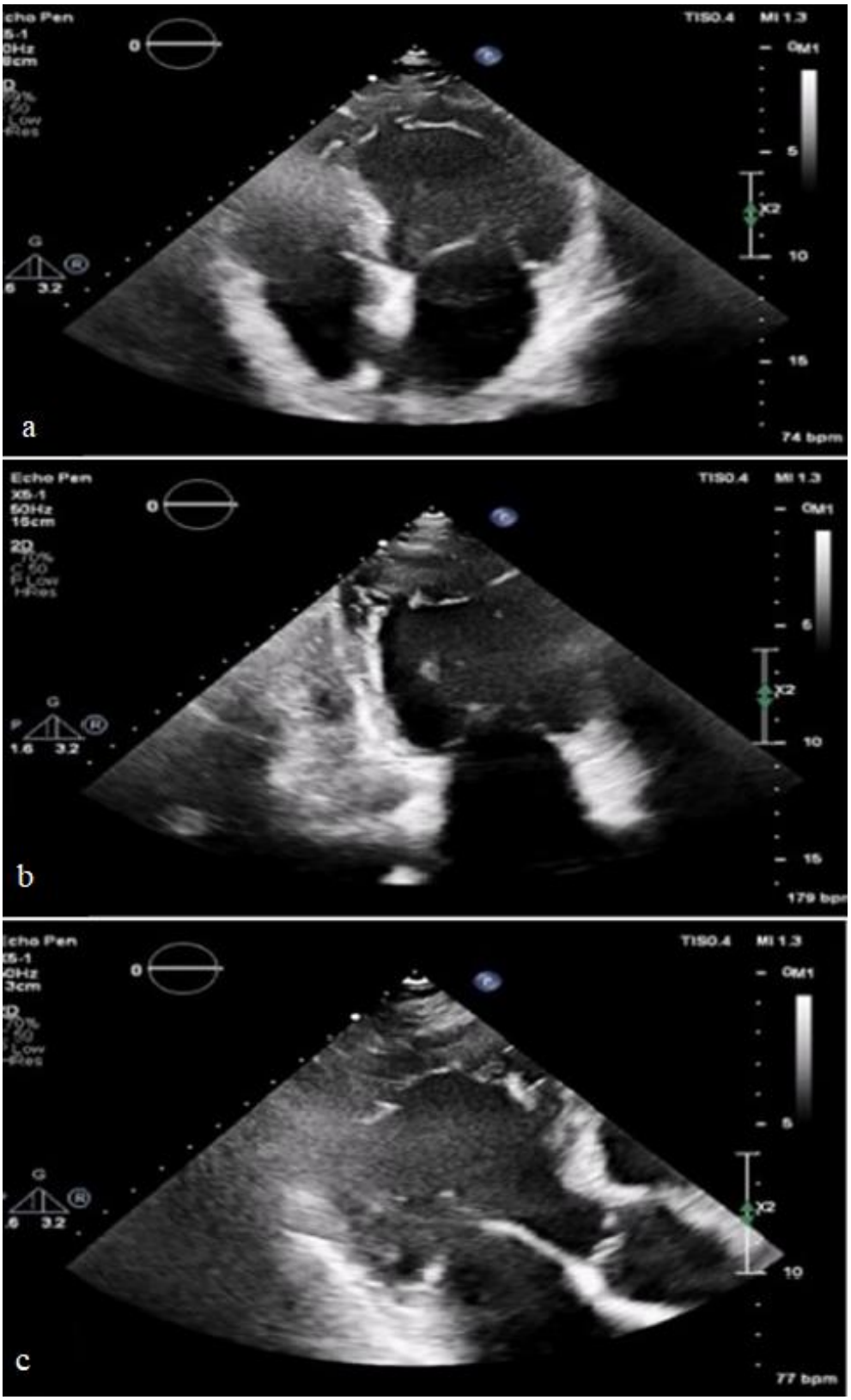

Fig. 2. Transthoracic echocardiography (TTE) – baseline assessment; apical views: a) 4-chamber, b) 2-chamber, c) 3-chamber (arrows – increased echogenicity of left ventricle endocardium).
Ryc. 2. Badanie echokardiograficzne przezklatkowe (TTE) – obraz wyjściowy; projekcje koniuszkowe: a) 4-jamowa, b) 2-jamowa, c) 3-jamowa (strzałki – wzmożona echogeniczność wsierdzia komory lewej).

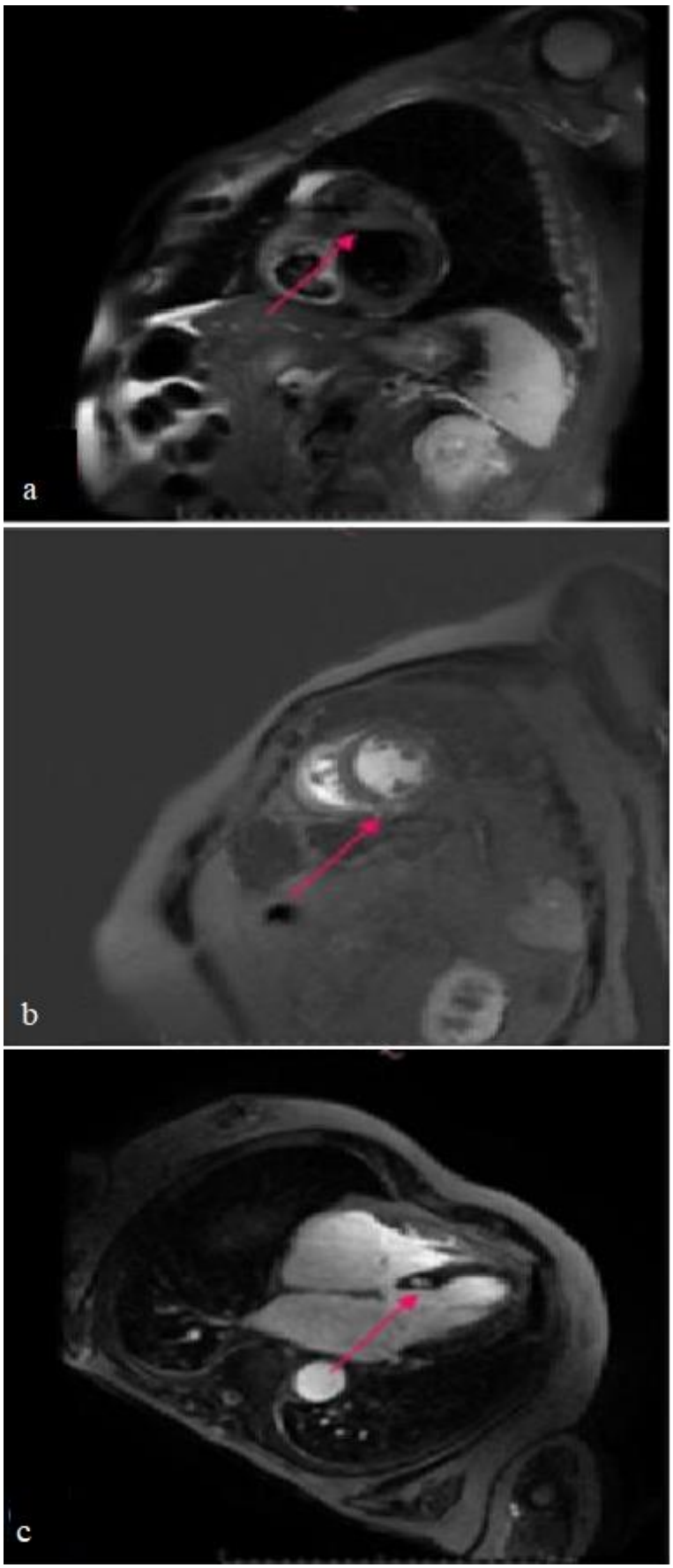

Fig. 3. Cardiac magnetic resonance (CMR) examination: a) T1-mapping – subepicardial late gadolinium enhancement (LGE) in basal segments of left ventricle; transversal view (arrow); b) T1-mapping – LGE localized in inter-ventricular septum; longitudinal view (arrow); without pericardial fluid, normal pericardial plaques.; c) T2-mapping (STIR sequence) – myocardial oedema in basal segments of left ventricle; transversal view (arrow).

Ryc. 3. Obrazowanie za pomocą rezonansu magnetycznego serca (CMR): a) T1-mapping – obecność podnasierdziowego późnego wzmocnienia pokontrastowego (LGE) w segmentach podstawnych lewej komory w projekcji poprzecznej (strzałka); b) T1-mapping – obecność LGE w segmentach przegrody międzykomorowej w projekcji poprzecznej (strzałka); c) T2-mapping (sekwencja STIR) – cechy obrzęku miokardium ściany przedniej komory lewej w projekcji podłużnej (strzałka); bez płynu w worku osierdziowym, prawidłowe blaszki osierdzia.

Considering the toxic effect of pembrolizumab as the most likely cause of myocarditis, the diagnosis and treatment decisions were made guided by the 2022 European Society of Cardiology (ESC) guidelines on cardio-oncology [11]. The criteria for clinical diagnosis are presented in Table II. The patient was started on steroid therapy as soon as possible, with methylprednisolone 1000 mg intravenously once daily for the first 3 days. There was improvement in the laboratory tests, with reductions in the troponin T, creatine kinase myocardial band (CK-MB) and transaminases values (Table III). It was decided to change the form of steroid therapy to oral. During hospitalization, anticoagulant, ventricular rate controlling AF, combined hypotensive, hypolipemic and gastroprotective pharmacotherapy were administered. The patient was discharged home in stable condition, with recommendations for further treatment in ambulatory patient care.

Table II. Diagnostic criteria for diagnosis of myocarditis as type of cardiotoxicity associated with cancer therapy, based on European Society of Cardiology (ESC) guidelines
Tabela II. Kryteria diagnostyczne zapalenia mięśnia sercowego jako rodzaju kardiotoksyczności związanej z terapią przeciwnowotworową, na podstawie wytycznych Europejskiego Towarzystwa Kardiologicznego (ESC)

Clinical diagnosis	
increased troponin levels and 1 major or 2 minor criteria	
major criterion	minor criteria
CMR	clinical manifestations
	ventricular arrhythmia
	deterioration of LV systolic function, contractile dysfunction other than TTS
	other immunological side effects (myositis, myasthenia gravis, myopathy)

CMR – cardiovascular magnetic resonance; LV – left ventricle; TTS – Takotsubo syndrome

Table III. Comparison of laboratory tests performed during 5 days of patient's hospitalization in Department of Cardiology
Tabela III. Porównanie badań laboratoryjnych wykonanych w ciągu 5 dni hospitalizacji pacjenta na oddziale kardiologii

Type of laboratory test	1. day	2. day	3. day	4. day	5. day
Troponin T	0.500 ng/ml	0.363 ng/ml	0.307 ng/ml	–	–
CK-MB	205 U/l	–	–	–	71 U/l
ALT	246 U/l	–	–	–	200 U/l
AST	275 U/l	–	–	–	74 U/l
Creatinine	0.93 mg/dl	–	–	–	0.84 mg/dl

CK-MB – creatine kinase myocardial band; ALT – alanine aminotransferase; AST – aspartate aminotransferase

DISCUSSION

Immunotherapy has in its arsenal monoclonal antibodies that interfere with so-called immune checkpoints [4,7]. An example of an immune checkpoint inhibitor (ICI) of PD-L1/PD-1 is pembrolizumab [6,7]. Blocking PD-1 prevents it from binding to its partner protein on the T lymphocyte, resulting in inhibition of the immune system's self-tolerance to tumor antigens, resulting in recognition of the tumor and promotion of its elimination [7,11]. Their expression occurs in T and B lymphocytes, thymic T cells, Langerhans cells, the eye, testes, and cardiomyocytes [7]. The therapeutic activity of ICI, by altering immune tolerance, can result in inflammatory side effects (immune-related adverse events – IRAEs) [7]. The pathogenesis of adverse effects is complex, at the molecular level involving an increase in intracellular calcium overload, increased inflammation through increased expression of nuclear factor kappa B (NF-kB), interleukin B4 (IL-B4), interferon gamma (IFN-γ), granzyme B, and tumor necrosis factor alpha (TNF-α) [7]. The adverse effects described in the literature include type 1 diabetes, hepatitis, thyroiditis, pancytopenia, colitis, keratoacanthoma, scleroderma, myasthenia gravis, and uveitis [6,7,10]. Cases of cardiotoxicity have also been described, e.g. in the form of acute coronary syndrome, atrioventricular block, supraventricular and ventricular arrhythmias, sudden cardiac death, myocarditis, Takotsubo syndrome (TTS), non-inflammatory left ventricular dysfunction, pericarditis, and pericardial effusion [6,12,13].

In the described case, two significant adverse effects can be distinguished in the patient – hepatotoxicity and cardiotoxicity. Elevated liver enzyme levels indicate

liver damage. In the described case, when differentiating the causes of hypertransaminasemia, the possibility of the occurrence of tumor metastases in the liver, hepatotoxicity of the administered immunotherapy, coexisting diseases, and coronavirus disease 2019 (COVID-19) infection should be taken into account. No liver metastases were detected in the patient under consideration. During the course of COVID-19, liver parameters may be slightly elevated. In a review study by Ammirati et al. [14], the maximum alanine aminotransferase (ALT) value in patients with myocarditis in the course of COVID-19 was 83 U/l, whereas in the case under discussion, it was as high as 246 U/l. Additionally, the described patient was diagnosed with cholelithiasis, which could also account for such elevated liver parameters. The diagnosis of the described patient was carried out in accordance with the 2022 ESC guidelines on cardio-oncology. Cardiotoxicity induced by pembrolizumab has been observed both in patients with pre-existing cardiac conditions as a result of immunotherapy, as illustrated in the case presented here, as well as in patients without a history of heart disease, as demonstrated in the case described by Sh Ahmed et al. [15]. The described patient has a long medical history of sustained AF, a history of ischemic stroke 1 year before the current event, and hyperlipidemia. The described patient, according to ESC guidelines, is categorized as high risk. In accordance with ESC guidelines, the described patient underwent a series of diagnostic tests before the commencement of immunotherapy. Among biochemical tests, troponin T and CK-MB markers were measured. ECG was performed. TTE visualized a slight enlargement of the right ventricle, with no other significant abnormalities.

The analyzed patient showed no signs of infection with the most common viral or bacterial pathogens that cause myocarditis. In addition, there is no history of an autoimmune disease burden. The fact of asymptomatic COVID-19 infection and its possible influence on the development of myocarditis in the analyzed patient was submitted for consideration. COVID-19 binds with high affinity to the human angiotensin-converting enzyme receptor 2, which is widely expressed in the lungs and heart, among others in human body [16]. In the literature, there are data on patients with COVID-19 myocarditis who presented with a full--blown respiratory infection accompanied by cardiomegaly and decreased LVEF [16]. In analyzing the case of our patient, it is difficult to unequivocally determine the parameters that would allow us to determine whether the occurrence of myocarditis is a consequence of the recent viral infection or whether it is a side effect of the oncological treatment. Based on the findings of the review study, two issues seem to be helpful in this case – the parameters such as the size of the heart and the ejection fraction [14]. Myocarditis after PD-1 therapy is associated with a preserved normal ejection fraction and does not manifest itself in an increase in the dimensions of the heart (or their slight elevation). The diagnosis of COVID-19 myocarditis was rejected as more likely than ICI-dependent myocarditis.

Takotsubo syndrome was also considered in the differential diagnosis. The presence of cancer, ICI as anti-cancer therapy are recognized as predisposing factors to the occurrence of this type of cardiomyopathy [11]. Owing to the lack of fulfilled criteria, especially the confirmation of myocarditis in CMR, this diagnosis was rejected.

The first-line of treatment for ICI-associated myocarditis is steroid therapy, started as soon as possible to reduce major adverse cardiovascular events, including mortality [11]. In the study by Matsumoto et al. [17] a similar case of pembrolizumab-induced cardiotoxicity in a patient was successfully treated with high-dose corticosteroids with good effect. In the case study described here, intravenous methylprednisolone was started, followed by oral prednisone. Su et al. [18] suggest that steroid therapy should be individualized to balance the beneficial effects and adverse effects of immunosuppression. In the case of the described patient, the used dose of steroid therapy resulted in a significant reduction in the values of myocardial necrosis markers, including aminotransferases, illustrating the extinction of the autoimmune process induced by ICI in the liver. Lyon et al. [11] describe cases of patients when systemic steroids are ineffective. Jang et al. [19] present a 48-year-old female patient with metastatic thymoma, who experienced fulminant myositis with cardiotoxicity after receiving one cycle of pembrolizumab treatment. Despite the immediate administration of systemic steroids, the patient's muscle weakness and hypercapnia did not improve. However, the patient recovered fully after undergoing plasma exchange therapy. This case highlights the importance of considering immunoglobulin G administration and plasma exchange as the next course of treatment for steroid-refractory patients. It underscores the significance of recognizing IRAEs, including those affecting the cardiovascular system in patients undergoing immunotherapy [19]. The general procedure is shown in Figure 4.

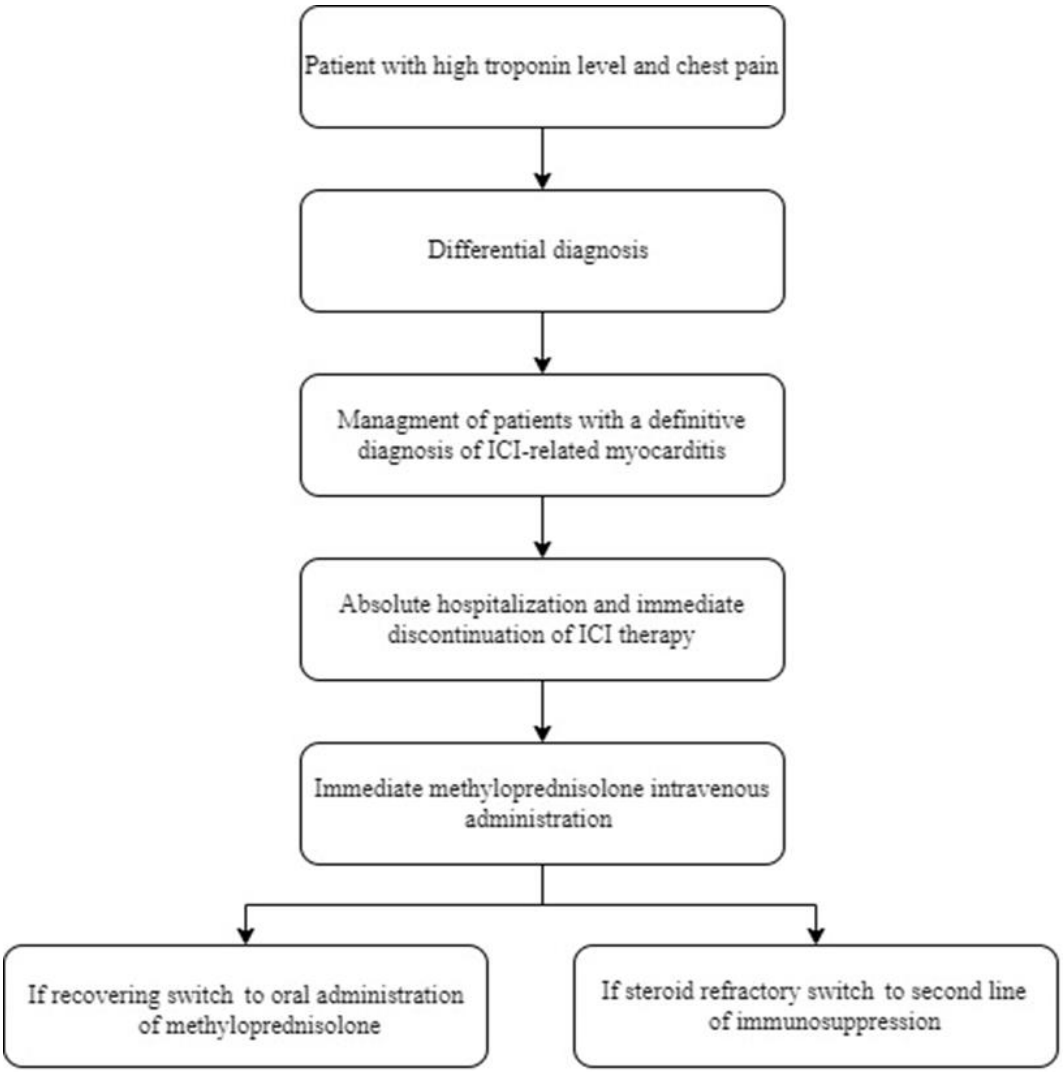

Fig. 4. Scheme of management in patients diagnosed with myocarditis in course of immune checkpoint inhibitor (ICI) immunotherapy based on European Society of Cardiology (ESC) guidelines.
Ryc. 4. Schemat postępowania u pacjentów z rozpoznanym zapaleniem mięśnia sercowego w przebiegu immunoterapii z zastosowaniem inhibitorów punktów kontrolnych (ICI) na podstawie wytycznych Europejskiego Towarzystwa Kardiologicznego (ESC).

In addition to pharmacological treatment, alternative methods should be considered. The case described in study by Hu et al. [20] demonstrates that timely pacemaker implantation may play a crucial role in improving the outcomes for patients with immune--related myocarditis. This suggests that patients with immune-related myocarditis, concomitant with cardiac conduction system disease, may benefit from the implantation of a pacemaker.

The patient was discontinued from ICI treatment at the stage of suspected cancer therapy-related cardiovascular toxicity (CTR-CVT). After withdrawal of the symptoms of ICI-associated myocarditis and the discontinuation of oral steroid therapy, discussion within the multidisciplinary teams (MDT) surrounding the patient's care is recommended to review the decision on whether to resume ICI treatment and conduct long-term follow-up, including the rapid identification of cardiovascular disease (CVD) risk factors [11].

The overarching goal of the discipline of cardio-oncology is to enable cancer patients to safely receive the best possible individualized anticancer treatments, minimizing CTR-CVT across the continuum of care [11].

Author's contribution

Study design – G.B. Orzeł, M. Łydka, J. Lewandowska, J. Stachowiak, E. Szymańska, K. Mizia-Stec
Manuscript preparation – G.B. Orzeł, M. Łydka, J. Lewandowska, J. Stachowiak
Literature research – G.B. Orzeł, M. Łydka, J. Lewandowska, J. Stachowiak, E. Szymańska, K. Mizia-Stec
Final approval of the version to be published – K. Mizia-Stec

REFERENCES

1. Pilleron S., Soto-Perez-de-Celis E., Vignat J., Ferlay J., Soerjomataram I., Bray F. et al. Estimated global cancer incidence in the oldest adults in 2018 and projections to 2050. Int. J. Cancer 2021; 148(3): 601–608, doi: 10.1002/ijc.33232.

2. Pilleron S., Sarfati D., Janssen-Heijnen M., Vignat J., Ferlay J., Bray F. et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study. Int. J. Cancer 2019; 144(1): 49–58, doi: 10.1002/ijc.31664.

3. Chaturvedi V.K., Singh A., Singh V.K., Singh M.P. Cancer nanotechnology: A new revolution for cancer diagnosis and therapy. Curr. Drug Metab. 2019; 20(6): 416–429, doi: 10.2174/1389200219666180918111528.

4. Chaft J.E., Rimner A., Weder W., Azzoli C.G., Kris M.G., Cascone T. Evolution of systemic therapy for stages I–III non-metastatic non-small-cell lung cancer. Nat. Rev. Clin. Oncol. 2021; 18(9): 547–557, doi: 10.1038/s41571-021-00501-4.

5. Reck M., Rodríguez-Abreu D., Robinson A.G., Hui R., Csőszi T., Fülöp A. et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small cell lung cancer. N. Engl. J. Med. 2016; 375(19): 1823–1833, doi: 10.1056/NEJMoa1606774.

6. Upadhrasta S., Elias H., Patel K., Zheng L. Managing cardiotoxicity associated with immune checkpoint inhibitors. Chronic Dis. Transl. Med. 2019; 5(1): 6–14, doi: 10.1016/j.cdtm.2019.02.004.

7. Varricchi G., Galdiero M.R., Marone G., Criscuolo G., Triassi M., Bonaduce D. et al. Cardiotoxicity of immune checkpoint inhibitors. ESMO Open 2017; 2(4): e000247, doi: 10.1136/esmoopen-2017-000247.

8. Gadgeel S., Rodríguez-Abreu D., Speranza G., Esteban E., Felip E., Dómine M. et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. J. Clin. Oncol. 2020; 38(14): 1505––1157, doi: 10.1200/JCO.19.03136.

9. Mascolo A., Scavone C., Ferrajolo C., Rafaniello C., Danesi R., Del Re M. et al. Immune checkpoint inhibitors and cardiotoxicity: An analysis of spontaneous reports in eudravigilance. Drug Saf. 2021; 44(9): 957–971, doi: 10.1007/s40264-021-01086-8.

10. Johnson D.B., Chandra S., Sosman J.A. Immune checkpoint inhibitor toxicity in 2018. JAMA 2018; 320(16): 1702–1703, doi: 10.1001/jama.2018.13995.

11. Lyon A.R., López-Fernández T., Couch L.S., Asteggiano R., Aznar M.C., Bergler-Klein J. et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur. Heart J. 2022; 43(41): 4229–4361, doi: 10.1093/eurheartj/ehac244.

12. Thakker R.A., Lee M.A., Albaeni A., Elbadawi A., Suthar K.H., Perez C. et al. Clinical characteristics and outcomes in immune checkpoint inhibitor therapy-associated myocarditis. Cardiol. Res. 2021; 12(5): 270–278, doi: 10.14740/cr1319.

13. Läubli H., Balmelli C., Bossard M., Pfister O., Glatz K., Zippelius A. Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. J. Immunother. Cancer 2015; 3: 11, doi: 10.1186/s40425-015-0057-1.

14. Ammirati E., Lupi L., Palazzini M., Hendren N.S., Grodin J.L., Cannistraci C.V. et al. Prevalence, characteristics, and outcomes of COVID--19-associated acute myocarditis. Circulation 2022; 145(15): 1123–1139, doi: 10.1161/CIRCULATIONAHA.121.056817.

15. Sh Ahmed O., Mahadevia H., Manochakian R., Zhao Y., Salinas M., Khoor A. et al. A Case of full recovery from prolonged cardiac arrest after infusion with paclitaxel and pembrolizumab. Case Rep. Oncol. 2022; 15(3): 1063–1073, doi: 10.1159/000527205.

16. Agdamag A.C.C., Edmiston J.B., Charpentier V., Chowdhury M., Fraser M., Maharaj V.R. et al. Update on COVID-19 myocarditis. Medicina (Kaunas) 2020; 56(12): 678, doi: 10.3390/medicina56120678.

17. Matsumoto T., Fukuda K., Yoshida T., Shimazu K., Taguchi D., Shinozaki H. et al. Sudden and severe cardiotoxicity induced with pembrolizumab, its clinical course, therapeutic intervention, and outcome. Int. Cancer Conf. J. 2022; 11(1): 81–86, doi: 10.1007/s13691-021-00525-8.

18. Su L., Liu C., Wu W., Cui Y., Wu M., Chen H. Successful therapy for myocarditis concomitant with complete heart block after pembrolizumab treatment for head and neck squamous cell carcinoma: A case report with literature review. Front Cardiovasc. Med. 2022; 9: 898756, doi: 10.3389/fcvm.2022.898756.

19. Jang S.Y., Lee S.Y., Lee H.L., Choi J. Early development of pembrolizumab-induced fulminant myositis and cardiotoxicity in a patient with metastatic thymoma. Respirol. Case Rep. 2022; 10(9): e01025, doi: 10.1002/rcr2.1025.

20. Hu C., Zhao L., Zhou C., Wang H., Jiang S., Li Y. et al. Pacemakers and methylprednisolone pulse therapy in immune-related myocarditis concomitant with complete heart block. Open Med. (Wars) 2022; 17(1): 2109–2116, doi: 10.1515/med-2022-0611.