

MYOCARDITIS INDUCED BY IMMUNOTHERAPY: A rare but fatal complication.

Abstract

The emergence of immunotherapy and the gradual expansion of its indications in oncology will require particular vigilance to detect and quickly take care of the potential cardiac toxicities. They have improved prognosis and survival, including patients with kidney, lung or skin cancers (melanoma) and certain lymphomas. The incidence of unwanted cardiac events under immunotherapy is rare, undoubtedly less than 1 % under **Ipilimab, Pembrolizumab** and **Nivolumab**. Cardiac toxicity can be induced by many drugs but this time we will focus on myocarditis induced by immuno-modulators, which is a rare but very fatal complication and has 2 main parts: an illustration of a clinical case and a review of the literature comprising generality, pathophysiology, clinical manifestations, the diagnostic strategy and therapeutic management based on the guidelines of the European Society of cardiology on cardio-oncology recently published in 2022.

Keywords: Myocarditis, Immune check point inhibitors, corticosteroids.

Introduction

The introduction of immunotherapy (IMT) is a major therapeutic innovation in the treatment and management of cancer patients. They have improved prognosis and survival, including patients with kidney, lung or skin cancers (melanoma) and certain lymphomas [1]. Their administration, however, is engaged in variable gravity side effects that can bring the vital prognosis into play. These side effects are similar to autoimmune reactions secondary to uncontrolled activation of the immune system against itself which can theoretically touch all organs. These autoimmune or dysimmunitarian adverse effects can affect 70 to 90 % of patients treated with IMT when including all severity levels and affected organs [2,3].

Acute myocarditis, acute pericarditis, vasculitis, atrioventricular conduction disorder and ventricular rhythm disorder are the most frequently raised cardiac complications after the administration of immunotherapy.

This article will focus more on myocarditis induced by immuno-modulators, which is a rare but very fatal complication and has 2 main parts: an illustration of a clinical case and a review of the literature comprising generality, pathophysiology, clinical manifestations, the diagnostic strategy and therapeutic management.

A. Case Report

80 -year -old with cardiovascular risk factor; hypertension, dyslipidemia, overweight; Wearer of a CRT-D Sorin implanted device in 2010 as in primary prevention of a dilated hypokinetic rhythm cardiopathy, left ventricular ejection fraction (LVEF) 20% with persistent atrial fibrillation (AF), ablated in December 2018 with return to sinus rhythm whose last transthoracic echocardiography (TTE) in 2017 noted a dilated cardiomyopathy (DCM); VEF at 50- 55%. He was followed-up for Right Ureteral Epidermoid Carcinoma with multiples metastases at the bone, pulmonary, liver, peritoneal and cerebral regions under Pembrolizumab as second choice treatment.

Patient reported symptoms for 2 days, which he describes as palpitations with sudden appearance of a right visual deficit without headache for which he consults in the emergency room where the

regression of the deficit was noted in 30 minutes with complete disappearance 2 hours after arriving in the emergency room, ECG Noted a slightly rapid AF of 103 beats per minute. Brain computed tomography scan (CT scan) showed no significant intracranial lesion, then patient was transferred to oncology department where he presented an elevation of heart enzymes; troponines 70ng/l, motivating his hospitalization in the heart intensive care unit for further management.

On physical exam: patient lucid and coherent, audible and regular heart bruits, crackling in the basal region of the lungs, unilateral oedema of the right lower limbs without erythematosis.

Biological assessment showed kidney creatinine at 121 micromoles/L, potassium at 3.8mmol/l, Ultrasensible enzyme troponin at 90 ng/L, Creatinine Kinase 31, CRP 160, hemoglobin at 10.4 g/dl.

ECG showed an atrial fibrillation without repolarization disorder

Echocardiography: Left ventricular tele diastolic diameter (LVTDD) of 56 mm non dilated, hypertrophic, preserved ejection fraction of 60 % in bipolar Simpson plane with no kinetic disorder. Global longitudinal strain was -14 %, Dilated left atrium at 22 cm², slightly dilated ascending aorta, no significant aortic stenosis or regurgitation. Normal left ventricular filling volume, minimal mitral leakage and conserved right ventricular function with low probability of pulmonary hypertension.

He therefore underwent a coronarography which concluded atheromal coronary arteries with no significant lesion of the anterior intraventricular artery. In view of all these elements, the diagnosis of myocardial toxicity induced by immunotherapy was retained.

B. Literature Review

Generalites

The emergence of immunotherapy and the gradual expansion of its indications in oncology will require particular vigilance to detect and quickly take care of the potential cardiac toxicities. The first security data collected in the past five years have shown that the most frequent side effects were dermatological, endocrine, digestive and pulmonary [1].

Due to a lower incidence (<1%), the cardiovascular side effects of immunotherapy will be characterized later. The expected cardiological side effects will probably be two orders:

- Those linked to direct cardiac toxicity, quite similar to the damage observed in autoimmune diseases with cardiovascular tropism (pericarditis, myocarditis, conduction and rhythm disorders, etc.)

- Others linked to another toxicity, in particular endocrine, renal, hepatic or pulmonary which may induce secondarily a cardiological impact (rhythm or conduction disorders, heart failure, pulmonary hypertension, etc.) [3].

The incidence of unwanted cardiac events under immunotherapy is rare, undoubtedly less than 1 % under **Ipilimab**, **Pembrolizumab** and **Nivolumab** [1, 2, 3, 4]. The clinical presentations described are varied: myocarditis, pericarditis, rhythm disturbances and left ventricular dysfunction. The incidence of toxicity, including the occurrence of myocarditis, seems more frequent during the combination of **ipilimumab** and **nivolumab** (0.27 %) compared to **nivolumab** alone (0.06 %) [1].

Analysis of databases in the pharmaceutical industry in April 2016 included among the 20,954 treated patients: ten cases of myocarditis (a fatal case) under nivolumab alone (n = 17,620) and eight cases of myocarditis (five fatal cases) under combination therapy nivolumab and ipilimumab (n = 2,974) [3]. More recently, an American team described the study of a cohort of 35 patients who

developed autoimmune myocarditis [5]. The prevalence in this series is evaluated at 1.14 %. The risk is multiplied by a three-factor during the anti-PD1 and anti-CTLA4 association. Although myocarditis is a rare adverse event, it should be noted that about one in three cases has a pejorative evolution with up to 50 % mortality [1, 2, 3]. The post-mortem myocardial analyzes of two patients revealed significant T lymphocytic infiltration (CD4+, CD8+) of cardiomyocytes but also the conduction tissues (sinus node and atrioventricular node). It is therefore an inappropriate immune response against myocardium which possibly presented a common epitope with tumor cells.

The peak incidence of autoimmune myocarditis is observed more particularly between the first and the third injection of immunotherapy (15 to 30 days after the first injection). In more than half of the cases, cardiac toxicity was associated with muscle or hepatic involvement of grades 3 or 4. Extracardiac toxicity must therefore be a particular element of vigilance.

Apart from autoimmune myocarditis, the other cardiac manifestations observed during clinical immunotherapy trials represent less than 1 % of cases: high blood pressure, pericarditis, rhythm disorders, acute coronary syndrome [3, 7]. The study of a recent French multicentric cohort brought in 30 cases of cardiac toxicity during immunotherapy [8]. The toxicities described were not systematically related to autoimmune myocarditis. The various manifestations observed were as follows: Systolic dysfunction of the left ventricle (79 %), atrial fibrillation (30 %), ventricular rhythm disorders (27 %), conduction disorders (17 %), Tako-Tsubo type syndrome (14 %) and pericardial effusion (7 %). The median to the appearance of toxicity was 65 days (minimum two days, maximum 454 days) from the first injection of immunotherapy [8].

1. Pathophysiology

The anti-checkpoint immunotherapy are monoclonal antibodies directed against the control points of the immune system.

Currently, anti-checkpoints which are used in oncology target inhibitory receptors present on the surface of lymphocytes (CTLA4, PD1) or their ligands (PD-L1, ligand of PD1).

1A. Action mechanism of immune control points (checkpoints) and tumor exhaust for the immune response

Checkpoints are essential in the activation of cell activation process. The immune system control points are receptors that intervene in the modulation of the activation of immune cells in order to limit the duration and intensity of the immune reaction. On the surface of the same cell of co-activating receptors (which strengthen activation) and co-inhibitory receptors (which decrease activation) (Figure1) on the surface. It is the complex balance between activating signals and inhibitory signals that determine if an immune cell can be activated. Thus, when a T lymphocyte recognizes its specific antigen thanks to its antigenic receiver (TCR), it can only be activated if the various signals sent by its control points are in favor of an activation. This phenomenon is physiologically very important on a daily basis. It intervenes to prevent the risk of autoimmunity (inhibitory receptors) but also strengthen the activation of the immune system in the event of infection for example (activating receptors). It also makes it possible to prevent an excessive reaction from the immune system, when an immune response takes place, the inflammatory signals released in the microenvironment will promote the expression of ligands of inhibitory receptors by nearby cells in order to avoid Immune reaction [8].

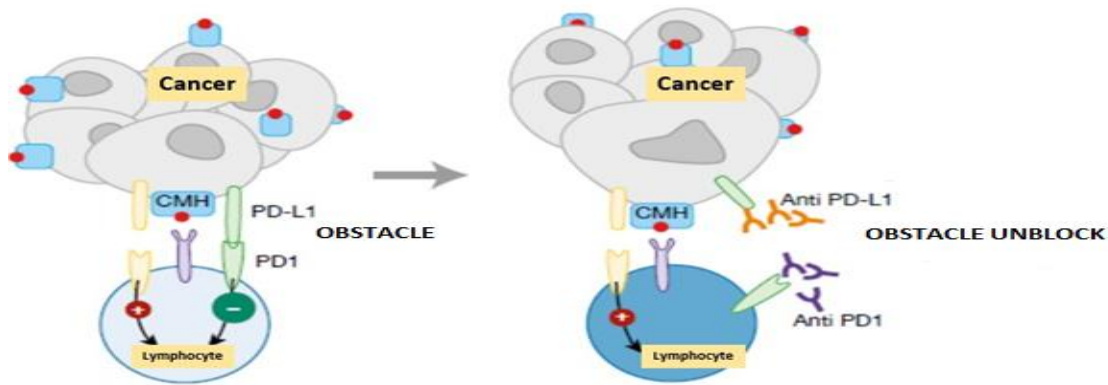


Figure 1: showing the tumor inhibits the lymphocytes by the PD1 receiver (left diagram) and inhibitory retro control blockage by the anti PD1 and anti PDL-1 inhibitor (right diagram) [9].

The cancer cells are capable of diverting the checkpoint system to their advantage. The tumor cells are capable of overexpressing on their surface the ligands of the inhibitory receptors to escape the immune system thanks to 2 regulation mechanisms:

- a-** Primary resistance: because of its mutations, the tumor cell begins to express naturally inhibitory ligands,
- b-** Secondary resistance occurs in reaction to an attack by the immune system, when the tumor is attacked, the release of inflammatory cytokines (IFN γ) by immune cells in the microenvironment promotes the expression of inhibitory ligands on the surface of tumor cells.

Anti-checkpoints make it possible to reverse the immunosuppression induced by the tumor.

Currently, anti-checkpoints that are used in cancerology target inhibitory receptors:

- CTLA4 (cytotoxic t lymphocyte associated antigen 4),
- The PD1 (Programmed Cell Death Protein 1) and its Ligand PD-L1.

1B. CYTOTOXIC T lymphocyte associated antigen (CTAL-4)

The first generation of anti-checkpoints targets the CTLA4. The CTLA4 is expressed at the CD8+ cytotoxic T lymphocytes but also at the Auxiliaries CD4+ and regulatory T. It intervenes early in the activation of T lymphocyte in the secondary lymphoid organs, during the presentation of the tumor antigen by the dendritic cell with naive T lymphocyte, by inhibiting the activation of the effector lymphocyte.

The CTLA4 molecules are present inside intracellular vesicles and are only transported to the surface of the lymphocyte when recognizing the specific antigen by the TCR. It is an early modulator of lymphocytic activation, the stronger the stimulation via TCR, the more the CTLA4 is produced in large quantities. The CTLA4, which is an inhibitory co-owner, has the same ligands as the activating co-owner CD28, CD80 and CD86. As CTLA4 has a stronger affinity for these ligands than CD28, it thwarts the activating effect of the CD28 and leads to inhibition of the lymphocyte [7].

1C. Programmed Cell Death Protein 1 (PD-1/PD-L1)

The second generation of anti-checkpoints targets the co-inhibitor receiver PD1 or one of its PD-L1 receptors. The Cell Death Protein 1 program (PD1) is another negative retro control which has the distinction of acting later in the process of activating lymphocytes, in the peripheral tissues and

tumor microenvironment. While the CTLA4 regulates the early activation of the naive T lymphocyte in the lymph nodes, the PD1 receiver acts in the activation of the T lymphocyte during its effective phase in contact with the tumor. Like the CTLA4, the PD1 is expressed at the CD4+ and CD8+ T lymphocytes and regulatory T. The PD1 receiver has two ligands, the PD-L1 (or B7-H1) and the PD-L2 (or B7-DC). Also, tumor analysis shows that the PD1/PD-L1 route is often used by tumors to escape the immune system, tumor cells often express the PD-L1 ligand on their surface. The use of antibodies directed against inhibitory co-receptions (anti-CTLA4, anti-PD1) or their receptors (anti-PD-L1) will make it possible to block the functioning of these receivers and thus prevent them from inhibiting the immune response. By raising the brakes of the immune system, an anti-tumor immune response was reactivated which was previously asleep (figure 2,3).

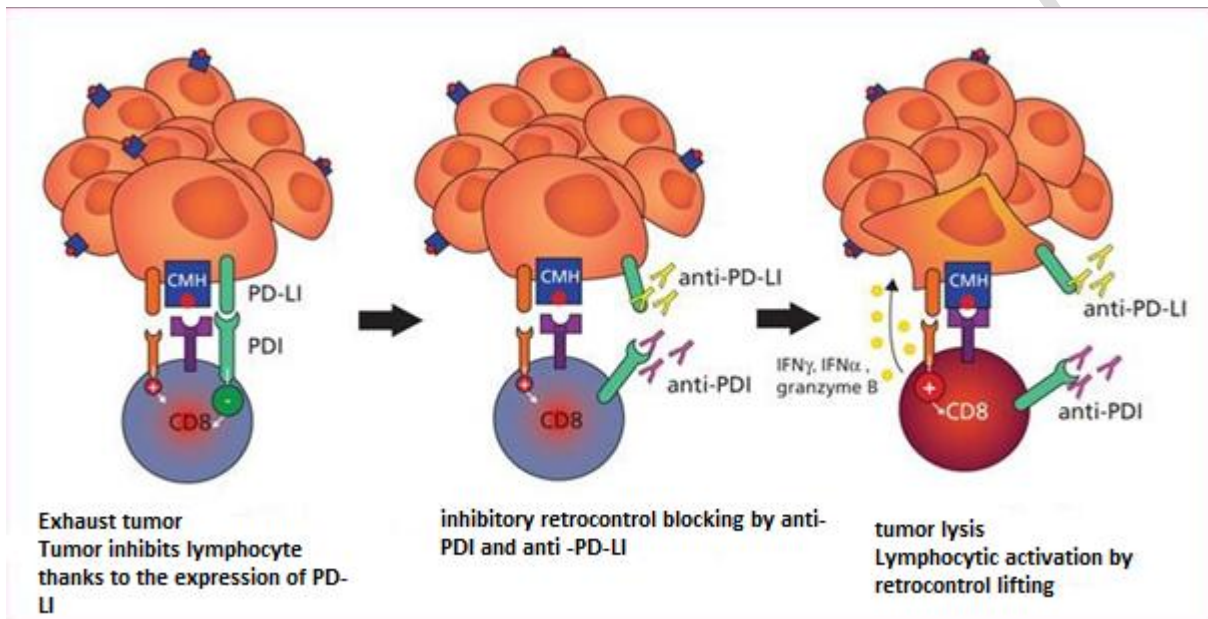


Figure 2: Action Mode of the Anti PD-1/PDL-1 [10].

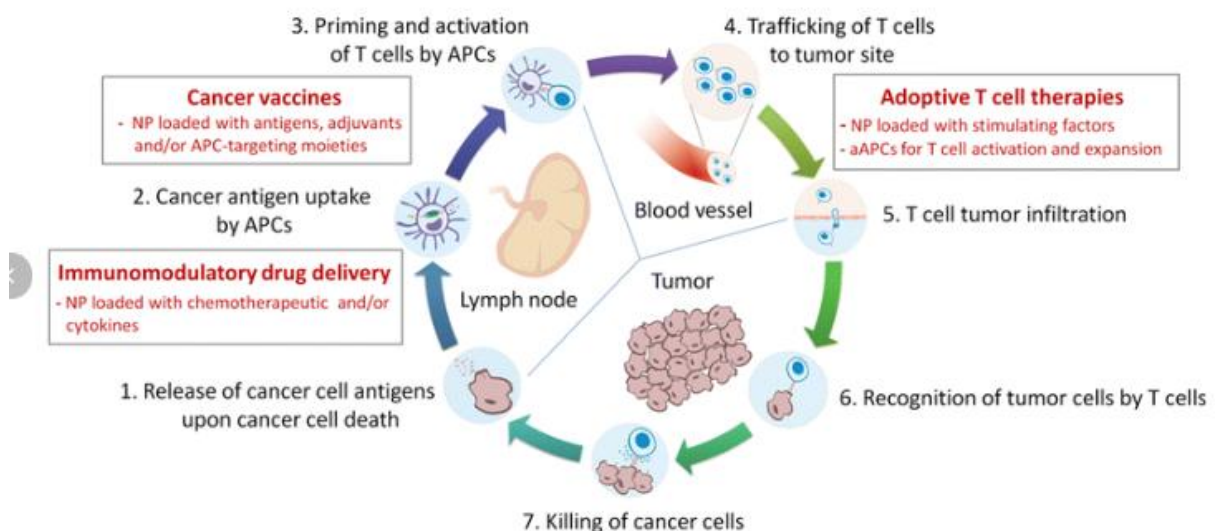


Figure 3: The 7 key stages of immunotherapy [11].

1D. Mechanisms of cardiac toxicity of immunotherapy

The pathophysiological mechanisms of myocarditis linked to immunotherapy were described in 2016 in 2 patients treated for melanoma and died of a high -degree conductive disorder and a refractory ventricular rhythm disorder, the result of the treatment with a treatment Combination of immunotherapy (**nivolumab and ipililumab**). Analysis of endomyocardial biopsies has shown that myocardium and conduction ways were the seat of infiltration made up of lymphocytes (CD3+, CD4+, and CD8+), and activated macrophages (CD 68+) associated with necrosis and oedema. The mechanism is explained by an antigenic mimicry mechanism with tumor cells and jaws of lymphocytic activation by lift of anti-tumor immunotherapy, lymphocytes recognize myocardial cells as non-self explaining lymphocytic infiltration in Myocardial fabric by biopsy analyzes (Figure3).

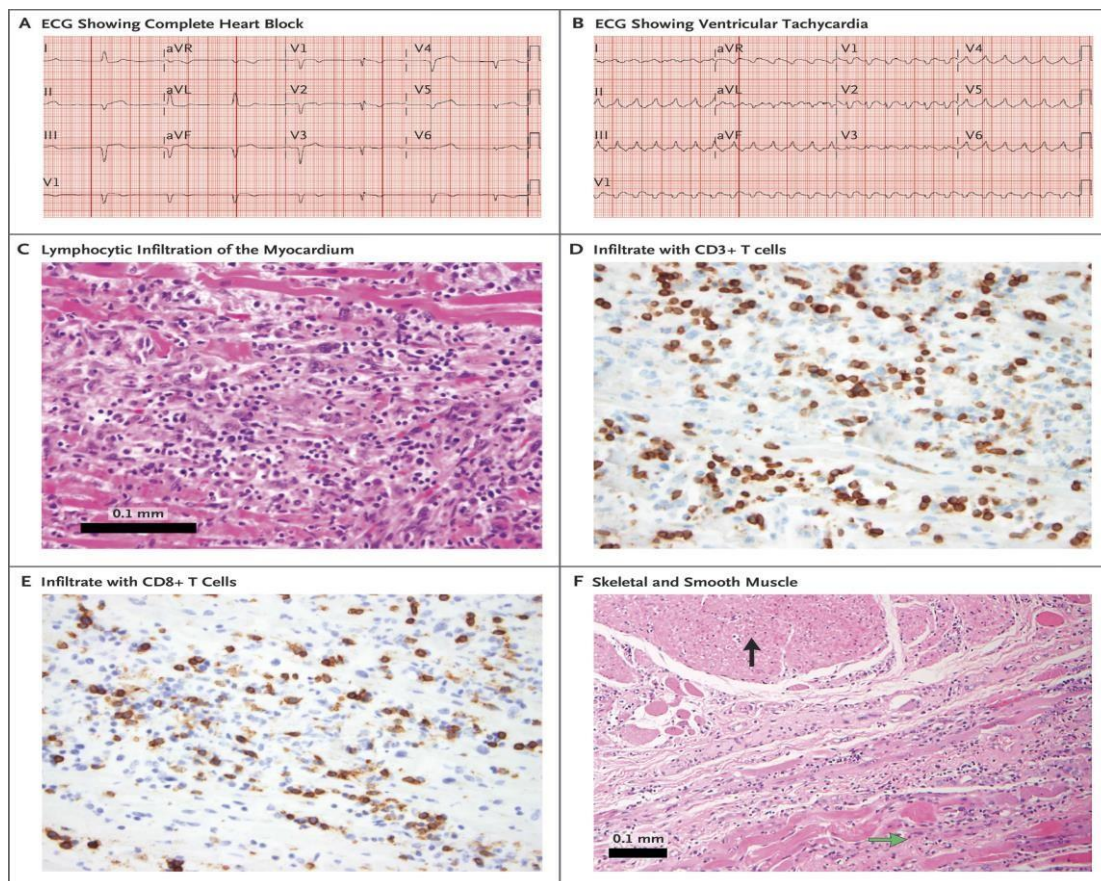


Figure 4: showing the massive infiltration of heart muscle by lymphocytes [12].

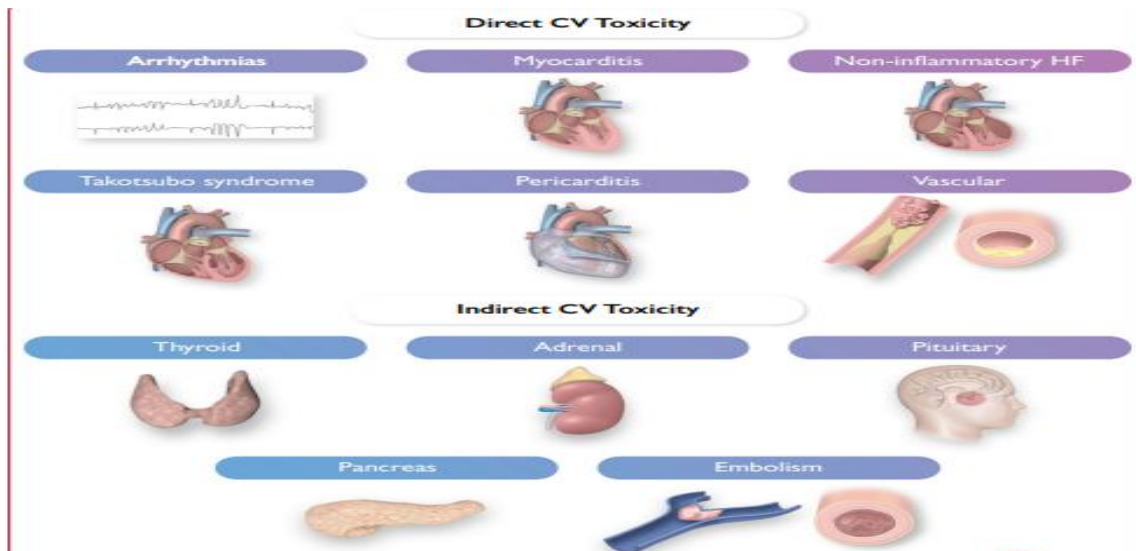


Figure 5: 7 Direct and indirect immune checkpoint inhibitor-related cardiovascular toxicity. CV, cardiovascular; HF, heart failure [13,14].

2. Clinical manifestations

The clinical manifestations of myocarditis to here can be divided into two clinical tables, fulminant myocarditis and the Pauci or Asymptomatic form

2A. Fulminant myocarditis:

It sometimes combines cardiogenic shock, ventricular rhythm disorders and sometimes requiring circulatory assistance. The clinical presentation is that of acute heart failure, due to acute pulmonary edema. It will be necessary to quickly recognize the clinical severity of the patients in front of a tachycardia (especially beyond 120 beats/min), a pinch, marbles, confusion or oliguria. You must also know how to identify a more deceptive table of low cardiac output not associated with signs of overload, or of predominant right heart failure. There are then, in addition to shock signs, digestive signs (abdominal, nausea pain).

Biologically, hyperlactatemia and renal failure are elements of gravity. Hepatic cytolysis, sometimes very important and then associated with a fall in prothrombin time (PT), can witness a cute damage liver. It is frequent in the event of cardiogenic shock and should not orient towards a primitive hepatobiliary etiology.

Additional examinations, ECG can show systematized disorders or not of cardiac repolarization and mimic an acute myocardial infarction, justifying the realization of a coronarography. A micro voltage linked to myocardial edema can be highlighted, as well as a PQ offset and diffuse ST segment depression in the event of associated pericarditis. Ventricular hyperexcitability or conduction disorders are possible.

At echocardiography, a thickening of the ventricular walls in relation to myocardial edema can be viewed; A pericardial effusion of variable abundance is often associated with it. The systolic ventricular ejection fraction is lowered, as well as the cardiac output and the systolic ejection volume. In this acute context, the left ventricle is not dilated, sometimes at the upper limit of normal. Heart wall motion disorders and the appearance of a left intraventricular thrombus are also possible. Troponin heart enzyme is almost always high, in a more or less marked way, a reflection of the importance of myocardial damage. The CRP is also very frequently high. The rise in creatinine, lactate

and transaminases enzymes indicates the impact of the shock. If the patient is transportable, myocardial MRI can help diagnosis and monitoring during follow -up.

2B. Asymptomatic form or pauci symptomatic form

This form sometimes makes the diagnosis difficult where the patient can be asymptomatic with sometimes normal paraclinical examinations sometimes leading to the realization of the endomyocardial biopsy to make the diagnosis. He can associate or have as an initial manifestation of extracardiac events of the autoimmune type.

3. Diagnosis Strategy.

Myocarditis induced by immunotherapy is a new entity whose clinical, biological and imaging characteristics differ from those of viral myocarditis. It most often occurs in the first 3 months following the establishment of immunotherapy and its diagnosis is complex, especially because there were no specific cardiological recommendations concerning the evaluation, monitoring and treatment of patients during immunotherapy treatment. Currently, in order to detect early cardiovascular side effects, the recommendations of ESC 2022 propose to rely on a surveillance protocol whose pace will be modulated according to the patient's risk level, evaluated on clinical, biological parameters and imaging (Figure 4).

Risk level	Test	Evaluation before treatment	Cycle 2	Cycle 3	Cycle 4	Every 3 cycles	Every 6 to 12 months
Low risk	Cardio-vasculaire Evaluation	X I				X I	X IIb
	ECG		X IIa	X IIa	X IIa	X IIa	X IIb
	TTE	X IIb					
	CTD	X I	X IIa	X IIa	X IIa	X IIa	
	BNP/ NT pro BNP	X I					X IIb
	High risk	Cardio-vasculaire Evaluation	X I				X I
High risk	ECG	X I	X IIa	X IIa	X IIa	X IIa	X I
	TTE	X I					
	CTD	X I	X IIa	X IIa	X IIa	X IIa	
	BNP/ NT pro BNP	X I					X I

Chart 1 : Protocol for monitoring a patient treated with IMT (indication of the examination and level of recommendation) [15].

This evaluation includes, the systematic realization of an electrocardiogram, a dosage of troponin, BNP or NT pro-BNP before starting immunotherapy in all patients at risk in order to avoid any diagnostic delay; High -risk patients should also be explored in addition by a transthoracic echocardiography. In monitoring all patients, whatever the risk level, it may be discussed, before each injection of immunotherapy, ECG and troponin dosage. This concerns patients with or not an underlying heart disease or having been exposed to other cardiotoxic treatments.

The diagnosis of a myocarditis induced by Immune check-point inhibitors (ICI) is complex. It is recommended to use the definition of the International Cardio-Oncology Society (IC-OS) in clinical practice (Chart 2), which is based, either on a diagnosis of certainty Histological derived from an endomyocardial biopsy, either on the combination of an elevation of the troponin level and a major criterion, or two minors, after having eliminated another cause (notably an acute coronary syndrome).

Test	Criterion in favor of the diagnosis
Endomyocardial biopsy	Lymphocytic infiltration and myocytic necrosis
Clinical diagnosis	Elevated troponin (significant or compared to the level before administration of the ICI) associated with a major criterion or 2 minor criteria after elimination of a differential diagnosis (ACS, TTS, cardiac metastasis etc.)

Major criterion: MRI criteria according to modified Lake Louise

Minor criteria:

Clinical presentation (Fatigue, myalgia, chest pain, diplopia, ptosis, dyspnea, orthopnea, limbs edema, syncope, fatigue, muscle, cardiogenic shock, cardiac arrest)

Ventricular rhythm and/or conduction disorder

Other immune-mediated impairment like myositis, myopathy, myasthenia gravis like syndrome

Alteration or degradation of LVEF, with or without heart wall motion abnormalities, not suggestive of a tako-tsubo syndrome.

MRI suggestive of the diagnosis: Presence of a modification of T1 or T2 in favor of myocardial inflammation in the presence of a compatible clinical presentation

Myocarditis
severity

Fulminant:

Hemodynamic instability, heart failure requiring non-invasive or invasive ventilation, high-grade or complete BAV and/or ventricular arrhythmia

Non-fulminant: including symptomatic patients but hemodynamically stable and without ventricular rhythm disorder and findings in patients with other immune-mediated adverse effects

Form refractory to corticosteroids: absence of resolution or worsening of clinical symptoms or persistent elevation of troponin despite high dose of corticosteroids

Chart 2 : Diagnostic criteria for myocarditis under IMT according to ESC 2022 [15].

The diagnosis or suspicion of myocarditis under here is carried in clinical practice, by the oncologist in charge of the patient. The degree of suspicion should be high in the face of a patient with clinical signs attracting attention to the cardiovascular device, such as chest pain, recent dyspnea, lipothymia or syncope. None of these signs are specific or sensitive, especially in the context of a patient with cancer.

The diagnosis should also be evoked or suspected in a patient with no cardiovascular symptoms but with signs and symptoms evoking an immune-mediated affection, such as hepatitis, myositis, a ptosis.

From clinical suspicion, the doctor prescribing immunotherapy will have to suspend immunotherapy, make an ECG, repeated plasma dosages of troponin and BNP/NT-pro BNP, then in the event of an anomaly detected, the patient should be quickly be address to the Heart team to ensure the monitoring and rapid implementation of examinations allowing a rapid diagnosis.

The ECG signs, as part of myocarditis, are not specific; Anomalies such as conduction disorders (atrioventricular block, branch block, elongation of the QT interval), rhythm disorders (ventricular or supraventricular) and repolarization anomalies (negative T waves, anomaly of the ST segment) may be recorded.

The diagnostic approach is based on the implementation of first line exams comprising a transthoracic echocardiography, which above all makes it possible to eliminate a differential diagnosis (pericardial effusion, anomalies of heart wall motions, cardiac metastases); Transthoracic echocardiography can be normal if myocarditis is not very extensive or during an early diagnosis. An ejection fraction normal of the left ventricle on the initial evaluation does not prejudice a favorable evolution [3]. The evolution of the most severe forms is made by the appearance of a systolic dysfunction with diffuse hypokinesis [16] and more rarely segmental. A low heart rate can be observed with the appearance of a state of cardiogenic shock.

A coronarography, perhaps carried out to eliminate a coronary occlusion, in this context it will not find coronary lesions that can explain the elevation of cardiac enzymes and left ventricular dysfunction which makes it possible to direct the diagnosis towards myocarditis.

A cardiac MRI, whose sensitivity is around 80 % in the event of immunological myocarditis [17], must be carried out, in the absence of hemodynamic instability, because it brings specific signs. It highlights the following elements:

- A myocardial edema in T2 weighting,
- an increase in early raising of gadolinium in T1 weighting
- Focal lesions not systematized to a coronary territory in late time.

Endomyocardial biopsy can be proposed and carried out in an expertise center when the diagnosis could not have been shown after the first line tests. The myocardial biopsies of the right ventricle by endocavitic means are the examination of anatomo-pathological certainty if they are carried out in the pathological zone but are rarely practiced outside the severe forms.

4. Differential diagnostics

The differential diagnoses to be evoked are acute heart failure secondary to other triggers and the causes of chest pain with troponin elevation.

The main causes of troponin elevation are mainly acute coronary syndromes of type 1 (rupture of an atherothrombotic coronary plaque) and type 2 (myocardial ischemia secondary to an imbalance between oxygen and consumption intake). Troponin elevation can also be explained by other disease-causing myocardial lesions without ischemia (anthracyclines, trastuzumab) or extra-cardiac causes (sepsis, kidney failure, etc.).

Clinical examination, ECG, standard biology (CBC, CRP, CK, CK MB (more specific), creatininemia, etc.) and transthoracic echocardiography make it possible to eliminate the main differential diagnoses. Coronarography and cardiac MRI can be proposed on a case -by -case basis depending on the data of the first exams. Certain fundamental data make it possible to assume that blockages of cellular receptors by anti-PD1 or anti-CTLA4 could have consequences on the evolution of atherosclerosis [16].

5. Treatment

Any suspicion of myocarditis must lead to urgent hospitalization and investigations allowing a rapid diagnosis, including echocardiography, cardiac MRI and endomyocardial biopsy, if the results are contradictory, in order to ensure the lack of development Towards a fulminant form described previously [1]. The severity of myocarditis, based on clinical, hemodynamic presentation, and ECG, make it possible to classify patients in fulminant, non -fulminant and refractory forms requiring corticosteroid therapy.

From this initial evaluation, decision of hospitalization (intensive care unit) and the intensity of initial management, in particular immunosuppressive treatment (corticosteroids alone or association with an immunosuppressant) are carried out (figure 6).

There are currently no specific recommendations to take care of these patients and therapy will be based on the data obtained with other causes of autoimmune myocarditis [18]. Potentially usable second -line immunosuppressants are currently only a low level of evidence, but have shown their relevance of the series of monocentric study (tocilizumab, abatacept, alemtuzumab, and tofacitinib).

In the majority of cases, the ICIS will be definitively arrested after a multidisciplinary discussion.

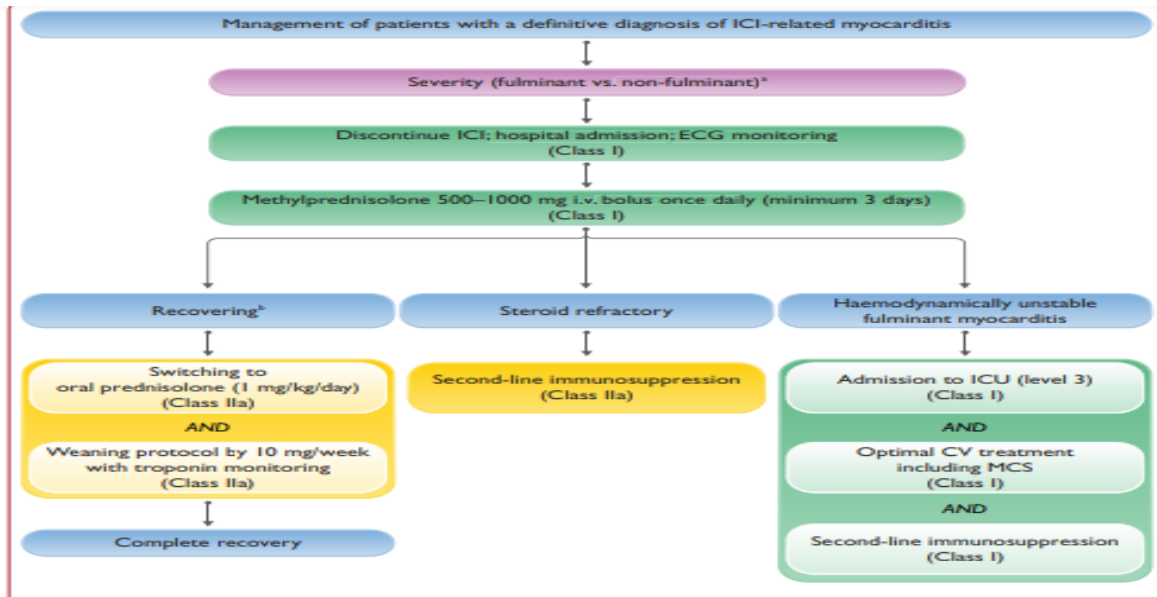


Figure 6: management of a patient with proven myocarditis secondary to the administration of an ICI [15].

Management of patients with rapid immunosuppressive treatment as soon as the diagnosis is highly likely by starting with methylprednisolone: 500 to 1000 mg per day in bolus for a period of at least three days then by prednisolone to 1 mg/kg/days orally and decrease of 10mg/week depending on the level of troponin [15,18,19] in case of recovery.

In the event of hemodynamic instability or severe heart failure, optimization of the treatment of heart failure is recommended and temporary circulatory assistance will be discussed as a multidisciplinary team in a patient with an advanced neoplastic disease [15].

Finally, in the event of cortico-resistance, second-line immunosuppressants like **Abatacept** can be considered [15,20, 21].

The resumption of immunotherapy will have to be discussed in the absence of an oncological alternative in certain cases of little severe toxicity and under close cardiological surveillance.

Our patient was treated with corticosteroids with a favorable clinical outcome since early diagnosis and intensive care was initially taken.

Conclusion

Autoimmune myocarditis is a rare cardiac complication related to immunotherapy. Its diagnosis can be misleading due to the frequency of atypical presentations, the diagnosis is based on the same criteria as myocarditis of other etiologies based on the combination of symptoms, ECG, Troponin, cardiac MRI and Endomyocardial Biopsy.

In the event of a clinical presumption, an urgent cardiological opinion is necessary to quickly guide the diagnostic and therapeutic management of the patient. The new guidelines of the ESC provide essential steps to follow in this case.

Abbreviations

BNP: Brain Natriuretic protein

CTLA4: cytotoxic T lymphocyte associated antigen 4,

CBC: Complete blood count

CK: Creatine kinase

CRP: C reactive protein

IFN γ : Interferon Gamma

NT pro BNP: Precursor of BNP

PD1: Programmed Cell Death Protein 1 and its Ligand PD-L1.

TCR: lymphocyte T cell receptor

References

1. Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugurel S, Thomas I, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016 ; 60:210–25.
2. 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 ; 21;3:11.
3. Tadokoro T, Keshino E, Makiyama A, Sasaguri T, Ohshima K, Katano H, et al. Acute Lymphocytic Myocarditis With Anti-PD-1 Antibody Nivolumab. *Circ Heart Fail*. 2016; 9 :e003514.
4. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. *N Engl J Med*. 2016; 375 :1749–55.
5. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, Sullivan RJ, Damrongwatanasuk R, Chen CL, Gupta D, Kirchberger MC, Awadalla M, Hassan MZO, Moslehi JJ, Shah SP, Ganatra S, Thavendiranathan P, Lawrence DP, Groarke JD, Neilan TG. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. *J Am Coll Cardiol*. 2018;71 :1755-1764
6. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36 :1714-1768.
7. Ferreira M, Pichon E, Carmier D, Bouquet E, Pageot C, Bejan-Angoulvant T et al. Coronary toxicities of anti-PD-1 and anti-PD-L1 immunotherapies: a case report and review of the literature and international registries. *Target Oncol*. 2018 ;13 :509-515.
8. Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, et al. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor-Related Cardiotoxicity. *Circulation*. 2017; 136 :2085–7.
9. Douglas B. Johnson, Caroline A. Nebhan, Javid J. Moslehi & Justin M. Balko. **Immune-checkpoint inhibitors: long-term implications of toxicity.** *Nature Reviews Clinical Oncology*. 2022 ; 19;254–267.

10. https://www.ncbi.nlm.nih.gov/books/NBK519842/figure/neuroendo_hypophysi.F4/
11. Michelle Graciotti, Crostaina Berti, Harm Antan Kloh, Lara Kadalaff. The era bioengineering. How will this affect the next generation of cancer immunotherapy. *Journal of Translation of medicine*. 2017: DOI- 10.1186/s12967-017-1244-2.
12. Douglas B. Johnson et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. *N Engl J Med* 2016; 375:1749-1755.
13. Dolladille C, Akroun J, Morice P-M, Dompmartin A, Ezine E, Sassier M, et al. Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: a safety meta-analysis. *Eur Heart J* 2021;42:4964–4977.
14. Zhang L, Reynolds KL, Lyon AR, Palaskas N, Neilan TG. The evolving immunotherapy landscape and the epidemiology, diagnosis, and management of cardiotoxicity: JACC: CardioOncology primer. *JACC CardioOncology* 2021;3:35–47.
15. After Lyon AR, 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
16. Courand PY, Croisille P, Khouatra C, Cottin V, Kirkorian G, Bonnefoy E. Churg-Strauss syndrome presenting with acute myocarditis and cardiogenic shock. *Heart Lung Circ*. 2012; 21:178–81.
17. Salem JE, Allenbach Y, Vozy A, Brechot N, Johnson DB, Moslehi JJ, Kerneis M. Abatacept for Severe Immune Checkpoint Inhibitor-Associated Myocarditis. *N Engl J Med*. 2019; 380:2377-2379.
18. Haanen JB, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol*. 2017;28: iv119-iv142.
19. Wang DY, Okoye GD, Neilan TG, Johnson DB, Moslehi JJ. Cardiovascular Toxicities Associated with Cancer Immunotherapies. *Curr Cardiol Rep*. 2017;19 :21.
20. Salem JE, Allenbach Y, Vozy A, Brechot N, Johnson DB, Moslehi JJ, Kerneis M. Abatacept for Severe Immune Checkpoint Inhibitor-Associated Myocarditis. *N Engl J Med*. 2019; 380:2377-2379.
21. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013; 34 :2636–2648, 2648a–2648d.