

Arrhythmias as a Complication of Chemotherapy

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Abstract:

The proposed review examines rhythm disturbances by the type of tachyarrhythmias, most often found in cancer patients, as well as their features, characteristic directly for oncological diseases, and emphasizes the importance of ECG monitoring for early diagnosis, treatment and monitoring of this cohort of patients who are more susceptible to the development of proarrhythmia. Oncologists should be fully aware of possible cardiac arrhythmias, and close cooperation between cardiologists and oncologists will lead to better stratification of the risk of developing cardiovascular diseases, monitoring and treatment.

Keywords: oncology, chemotherapy, arrhythmogenic effect, supraventricular tachycardia, ventricular tachycardia, cardioncology, cardiotoxicity.

Introduction

Introduction. A normal sinus rhythm, registered once on an ECG or with short monitoring, does not exclude the presence of hidden or even life-threatening disturbances of the rhythm and conduction of the heart. In the presence of clinical symptoms suspected of arrhythmia, but without explicit detection of arrhythmia during hospitalization, it is necessary to make every effort to search for a particular cardiac arrhythmia. At the same time, it should be remembered that sometimes we are dealing with "pseudo-arrhythmia" by which we need to understand artifacts or incorrect interpretation of ECG data. Chronic lung diseases, pleural or pericardial effusion, lung resection and radiation therapy of the chest or mediastinal organs, displacement of the heart during respiration and fibrosis can lead to positional changes in the electrical axis of the heart, RR intervals, QT interval, amplitude and width of the QRS complex, which can easily be mistaken for arrhythmia [1-4].

Characteristics of arrhythmia. Despite the fact that cardiac arrhythmias are most often classified according to their electrophysiological mechanisms, they can also be divided by etiological factor (the cause of arrhythmia). Arrhythmias of cardiac origin (primary) occur due to a particular pathology of the heart. The secondary genesis of cardiac arrhythmias, on the contrary, is due to metabolic imbalance, without obvious signs of structural pathology of the heart. This classification is rather conditional, because the heart of a patient weakened by a malignant neoplasm or aggressive treatment will be more sensitive to metabolic disorders and environmental factors, which can also induce cardiac arrhythmias.

In primary arrhythmias, the substrate is located in the cardiac and pericardial structures. This may be a limited pathological focus, for example, a necrosis site after a myocardial infarction, or a diffusely altered pathological zone in cardiomyopathies and infiltrative diseases, such as amyloidosis. Coronary artery disease, arterial hypertension and myocardial hypertrophy, dilated cardiomyopathy and fibrosis often lead to rhythm disturbances, both in patients with and without cancer. However, a number of diseases are more common in patients with cancer: these are primary and metastatic heart tumors, amyloid infiltration, pericardial pathology and cardiomyopathy associated with chemotherapy. Radiation therapy of the chest organs can also contribute to the occurrence of arrhythmia as a result of the formation of fibrosis sites, inflammation of the endocardium, myocardium or pericardium and progressive damage to the coronary arteries [5-8].

Secondary arrhythmias occur without any obvious structural pathology of the heart. Predisposing factors may be toxic effects of drugs, increased sympathetic tone, surgical interventions, hypoxia, release of inflammatory mediators and vasoactive kinins, and other metabolic disorders. The formation of an arrhythmogenic substrate can also be caused by the disintegration of the tumor and the cardiotoxic effect of chemotherapy. A carcinoid tumor can cause both primary and secondary arrhythmias: the production of metabolically active mediators leads to the formation of secondary arrhythmias, while the formation of endocardial infiltrates and valve damage is associated with the occurrence of primary arrhythmias [21-28].

Cardiac arrhythmias and conduction disturbances induced by taking antitumor drugs may be associated with both damage to cardiomyocytes (they can be considered primary) and with changes in metabolism due to this therapy (which may cause the development of secondary arrhythmias). In case of gross violation of internal homeostasis, it is necessary to conduct detailed monitoring of the heart rhythm, and in case of potentially life-threatening arrhythmias, it is necessary to modify the scheme of antitumor therapy. It should be noted that not only antitumor agents can lead to heart rhythm disturbances. In the process of treating a cancer patient, antibacterial drugs, psychotropic agents, antiemetics, hormonal drugs, electrolytes and radiation therapy are used, which, in turn, can stimulate a variety of cardiac arrhythmias. Below we will consider some types of cardiac arrhythmias [9-12].

Supraventricular arrhythmias. The substrate of supraventricular arrhythmia (SVT) is located above the level of the atrioventricular node (AV node). SVT can be permanent and paroxysmal. The symptoms depend on the frequency of ventricular contractions, the duration of arrhythmia and the degree of decrease in cardiac output during tachycardia. SVT can be manifested by palpitations, pulsation in the neck, discomfort in the chest, shortness of breath, increased sweating, a clinic of progressive heart failure, dizziness and fainting. These complaints are often attributed to the

manifestation of panic attacks before the detection of supraventricular rhythm disturbances.

Paroxysmal SVT is quite common in cancer patients, mainly as atrial fibrillation (AF). SVT occurs mainly in the older age group of patients, against the background of previous arterial hypertension, as well as in violation of homeostasis: multiple organ pathology, hemodynamic and metabolic

imbalance, increase in the level of catecholamines. It was also revealed that aggressive chemotherapy and stem cell transplantation can lead to the occurrence of SVT. Radiation therapy outside the limits of the location of the heart (for example, in patients with cervical cancer) is also capable of provoking SVT [13-17].

Sinus tachycardia. Sinus tachycardia is most common, and despite its clinical significance for cancer patients, it is rarely noticed. With sinus tachycardia, an ECG always detects a P wave with a morphology identical to the normal sinus rhythm. The main feature of sinus tachycardia is its gradual onset and cessation (the phenomenon of warming up and fading), which helps to distinguish it from SVT. The reasons for the development of this arrhythmia in cancer patients are obvious: pain syndrome, anxiety, fever, anemia, intoxication, hypovolemia, hypotension and pulmonary embolism. Since sinus tachycardia is a physiological reaction of the body to stress, its treatment (for example, with beta-blockers) is usually not justified and can worsen the patient's condition. It is important to detect the cause of sinus tachycardia in an oncological patient, and if possible eliminate it, rather than fight it.

Supraventricular extrasystole (SE). Supraventricular extrasystole is the most common supraventricular arrhythmia. In most cases, NZHE are benign asymptomatic arrhythmias that are common in the population and, in the absence of complaints of palpitations, do not need treatment. In cancer patients, it occurs after chemotherapy, during stress, with anemia, arteriovenous shunting of blood in the tumor, thyrotoxicosis, or may be associated with the development of a hyperadrenergic condition.

Paroxysmal SVT is an extensive group of arrhythmias with various mechanisms of occurrence. Unlike sinus tachycardia, they are characterized by a sudden onset and cessation, without the phenomenon of "warming up" and "fading". Most often, the frequency of ventricular contractions in this type of arrhythmia ranges from 100 to 300 beats per minute with equal R-R intervals.

Reciprocal paroxysmal SVTs are represented by atrioventricular nodular reciprocal tachycardia (AVRT), atrioventricular reciprocal tachycardia (AVRT) and rarely occurring sinus reciprocal and atrial tachycardia. Similar in the mechanism of occurrence of these tachyarrhythmias is the presence of an abnormal conducting system, which includes two (or more) pathways with different characteristics of the pulse rate and the refractory period. Also, a necessary condition for the induction of arrhythmia is the possibility of conducting the pulse anterograde along one of the paths and retrograde along the other, which leads to the formation of a mechanism for re-

entry of excitation or re-entry. These two paths can be dissociated anatomically (macro re-entry) as in Wolf-Parkinson-White syndrome (WPW) or be localized in one anatomical

zone (micro re-entry), for example, in the AV node in AVURT [14-18].

Arrhythmia is most often provoked by extrasystole, which occurs at a time when one of the pathways is still in the refractory period, and the other has already recovered and is capable of depolarization. In the presence of a substrate for the occurrence of SVT, an increase in the level of catecholamine leads to an increase in arrhythmia paroxysms due to changes in the electrical properties of the two re-entry pathways and an increase in the number of extrasystoles. Therefore, one of the types of SVT may manifest for the first time in oncological patients after a major surgical operation or during intensive chemotherapy.

The most common SVT is AVURT. The re-entry chain in this type of arrhythmia is localized inside or in the immediate vicinity of the atrioventricular node. The frequency of ventricular contractions in arrhythmia is 150-250 beats per minute and Fig. 2. Supraventricular tachycardia negative P waves are visible on the ECG in the terminal part of the QRS complex (usually in the II lead).

AVRT is a macro re-entry with two pathways, one of which is an AV node, and the other is an additional atrioventricular junction (DAVS). Usually, the pressure is capable only of retrograde conduction of impulses, at the same time, it is impossible to detect it on a normal sinus rhythm by ECG, since the pulse from the atrium to the ventricles usually occurs through the AV node (hidden pressure). If the pulse passes antegrade along the pressure, then signs of ventricular preexcitation appear on the ECG (an extended QRS complex due to a delta wave), which is typical for manifesting pressure. In this case, with tachycardia, retrograde P waves are noted, which are visible after ventricular complexes.

WPW syndrome deserves special attention for two unique reasons. Firstly, if during AVRT the pulse passes antegrade along the pressure, then the QRS complex expands and a broad-complex tachycardia (antidromic AVRT) will be presented on the ECG, which can easily be confused with ventricular tachycardia. In addition, when atrial fibrillation occurs, the rapid antegrade passage of pulses along the pressure (the phenomenon of non-incremental conduction) can lead to an excessively high rate of ventricular activation, ventricular tachyarrhythmia (even ventricular fibrillation) and SCD. In this case, drugs that inhibit the conduction in the AV node, such as digoxin or beta-blockers, are contraindicated, since due to the shortening of the refractory period of the pressure, the frequency of the ventricular response paradoxically increases. The drugs of choice for the relief of arrhythmia in this situation are Novocainamide, Amiodarone or electropulse therapy [19-20].

Several cases of WPW syndrome have been described in pediatric practice in tuberous sclerosis (Bourneville's disease) with the formation of cardiac rhabdomyomas. If these neoplasms have the ability to conduct impulses similarly to cardiomyocytes, and are

localized between the atrium and ventricle, crossing the fibrous ring of the heart, conditions are created for the formation of macro re-entry. Despite the fact that the theory of the occurrence of ventricular preexcitation due to rhabdomyoma is very controversial, a correlation was found between the localization of the tumor and the verified pressure during intracardiac electrophysiological examination. It should be noted that getting rid of AVRT occurred both with tumor resection and with radiofrequency ablation of the DAVS, there were also cases of spontaneous cessation of arrhythmic syndrome.

Multifocal atrial tachycardia - (MAT) is characterized by an irregular heartbeat of 100-300 beats per minute with 1:1 ventricular conduction and at least three different morphologies of the P wave with the absence of a dominant P wave. Differential diagnosis is carried out with sinus tachycardia with frequent supraventricular extrasystoles and atrial fibrillation; all these rhythm disturbances are due to an increased threshold of excitability of atrial tissue, and, it should be noted that MAT is often transformed into atrial fibrillation. However, it is necessary to clearly distinguish between these two types of arrhythmias, since the approaches to their treatment are completely different.

Ectopic atrial tachycardia is a rhythmic tachycardia with an atrial rate of 100-220 beats per minute and a morphology of the P wave different from the normal sinus rhythm. Cases of ectopic atrial tachycardia with atrial leiomyosarcoma and with the use of ifosfamide are described.

Atrial flutter and fibrillation - The cause of atrial fibrillation (AF) and atrial flutter (AFl.) is an electrical and mechanical imbalance of the atria. The clinical aspects and treatment strategies of these arrhythmias have a number of differences, but, in fact, they are largely similar. Therefore, we will consider them together. As noted earlier, these arrhythmias are common in cancer patients. Both at the moment of paroxysm of arrhythmia, and after the restoration of the sinus rhythm, mechanically the atria cannot work effectively (there is no atrial systole). This leads to stagnation of blood in the atria and creates conditions for the formation of atrial thrombi, and subsequently leads to thromboembolic complications. The most frequent place of formation of blood clots is the ear of the left atrium.

On an ECG, a typical atrial flutter is represented by regular atrial activity (F waves) with a frequency of about 300 beats per minute. The fluttering waves are asymmetric, have a sawtooth configuration, which is most clearly traced in the second lead.

AF is usually easily recognized on an ECG. It is characterized by irregular irregular atrial and ventricular activity. The frequency of ventricular response depends on the conduction in the atrioventricular node and varies in a wide range.

The clinical symptoms of AF are diverse, both in cancer patients and in patients without cancer. This may be an accidental finding during examination, in the case of an asymptomatic course of the disease, and may lead to severe hemodynamic instability with the development of acute heart failure. Symptoms, as a rule, depend on the frequency of ventricular contractions and the presence of atrioventricular dissynchrony. Paroxysms of AF, as a rule, are accompanied by a feeling of palpitation and lack of air [29-35].

Atrial fibrillation and fluttering are usually a manifestation of the underlying heart disease. Conditions in which the volume of the atria increases lead to an increase in atrial pressure, which forms atrial arrhythmias. Other risk factors are age, hypertension, lung diseases, thyrotoxicosis, surgical interventions and other conditions associated with increased catecholamine levels. In case of first-time AF or TP in cancer patients, it is necessary to exclude the symptomatic genesis of arrhythmia (pulmonary embolism, acute or chronic pericarditis, infection, thyrotoxicosis or other metabolic disorders), regardless of the presence of the underlying heart disease [32-37].

AF is associated with an increase in the level of C-reactive protein, which indicates a possible role of systemic inflammatory processes in the formation of an arrhythmia substrate in the left atrium. This theory was demonstrated directly in cancer patients; examination of patients with colorectal cancer in the absence of gross structural pathology of the heart and other risk factors revealed a threefold increase in the incidence of AF compared with the control group. After elective colectomy, AF developed in 4.4% of patients. This percentage was higher in the group with laparotomic surgical access. Moreover, the increased level of neutrophils in the first day after surgery was an independent predictor of the development of AF. The presumed mechanism of such a high frequency of AF may be systemic inflammation. Also, many chemotherapeutic drugs increase the likelihood of this arrhythmia (for example, gemcitabine, docetaxel, alemtuzumab, 5-fluorouracil, doxorubicin, cisplatin, melphalan). When they are used in the genesis of arrhythmia, a cardiotoxic effect cannot be excluded, but the role of systemic inflammation is also great [16-20].

Ventricular arrhythmias. This group of rhythm disorders includes ventricular extrasystoles, trigger and reciprocal (by the mechanism of re-entry) ventricular tachycardia. These arrhythmias are characterized by wide complexes of QRS on the ECG.

With cancer, the risk of ventricular arrhythmias increases; often in this group of patients there is a structural heart disease, as well as additional risk factors, such as the use of cardiotoxic antitumor drugs, which may be arrhythmogenic, as well as hormonal and metabolic imbalances, leading to ventricular arrhythmias.

Ventricular extrasystole (VE) is the most common ventricular arrhythmia, which is often found in healthy people without structural heart disease and in this case does not

pose any danger. In cancer patients, the number of RE may increase with a violation of homeostasis. Only in the presence of an underlying heart disease, the VE is associated with the development of life-threatening ventricular arrhythmias. Clinically, VE may be asymptomatic, be an accidental finding during an ECG or XM-ECG, or manifest as a feeling of palpitation, or dizziness, especially with frequent extrasystole due to a decrease in the number of effective ventricular contractions. Previously, VE was considered a dangerous rhythm disorder that always requires treatment, but later studies have shown that diligent attempts to suppress ectopia are more dangerous than the arrhythmia itself. Thus, RE does not require specific therapy, with the exception of patients with poor arrhythmia tolerance. The drugs of choice in this situation are beta-blockers, which, as a rule, are effective and do not have a proarrhythmic effect [21-28].

Ventricular tachycardia (VT) is a tachycardia with wide QRS complexes at a rate of more than 120 beats per minute (Fig. 7), the substrate of which is localized in the ventricular myocardium. Due to rapid and disorganized ventricular activity, which disrupts cardiac output and can lead to SCD, ventricular arrhythmias are much more life-threatening rhythm disturbances than SVT. A separate type of VT is tachycardia of the pirouette type (Torsades de pointes), which is characterized by specific risk factors, different ECG morphology and treatment tactics. VT usually begins with a VE, which occurs during a vulnerable period of the cardiac cycle.

Many chemotherapeutic drugs increase the likelihood of developing gastrointestinal tract, for example, interleukin, doxorubicin, rituximab, trastuzumab, thalidomide.

Ventricular fibrillation (VF) is characterized by chaotic, low-amplitude electrical activity on an ECG. With this arrhythmia, there is no mechanical activity of the heart, respectively, perfusion of organs stops. Complete hemodynamic collapse and death are inevitable if the sinus rhythm is not restored within a few minutes (spontaneous relief of arrhythmia or electrical cardioversion). Risk factors for VF are similar to VT, it should also be remembered about the possible transformation of stable high-frequency VT into VF with coronary circulatory insufficiency or severe metabolic disorders (for example, severe hypoxia). Treatment of VF is carried out according to the protocol of stable hemodynamically significant VT. Unfortunately, the effectiveness of resuscitation in cancer patients is lower than in the general population.

Tachycardia of the "Pirouette" type is a special type of polymorphic VT associated with congenital or acquired prolongation of the QT interval. Torsades de pointes literally means "twisting on pointes" (we are talking about the regularly changing morphology of QRS complexes), which characterizes the constantly changing shape, amplitude, direction of ventricular complexes: they seem to twist around an isoline. Despite the fact that this arrhythmia is usually stopped spontaneously, a transformation

into a stable VT or VF can occur, therefore it is considered a potentially life-threatening rhythm disorder. The frequency of ventricular contractions is about 200-250 beats per minute.

The QT interval is measured in one of the ECG leads with the maximum length of the distance from the beginning of the QRS complex to the final part of the T wave located on the isoline. Since the QT interval varies depending on the heart rate, a corrected QT interval (QTc) is used to estimate it: the QT interval divided by the square root of the RR interval measured in msec. Also, the normal value of the QT interval depends on the gender of the patient (normally the QTc is 340-450 msec for women and 340-430 msec for men). Prolongation of the QT interval of more than 500 ms, regardless of the patient's gender, is associated with a high risk of developing pirouette tachycardia. With an increase in the QT interval by 60 msec compared to the primary measurement of the interval, the risk of life-threatening arrhythmias also increases [20].

Therefore, with the prolongation of the QT interval of more than 500 msec when using drug therapy, it is necessary to assess all the risks, adjust therapy: prescribe an alternative drug, eliminate hypokalemia, evaluate the interaction of all drugs used.

The risk factors for pirouette tachycardia and prolongation of the QT interval are similar. This article does not consider the congenital forms of the extended QT interval, which are channelopathies. In cancer patients, prolongation of the QT interval is not uncommon, and often occurs when prescribing chemotherapy drugs. It should also be noted that concomitant pathology (diabetes mellitus, bradiarrhythmias, myocardial ischemia, heart failure, infections, cerebral circulation disorders), cachexia, hypothermia, electrolyte imbalance and drug polypragmasia make this cohort of patients particularly susceptible. Consequently, patients with oncology and concomitant cardiovascular pathology are at high risk of developing life-threatening tachyarrhythmias.

Drugs that lengthen the QT interval, which are often used in cancer patients, are listed in the table. According to studies in palliative care units (hospices), the QT interval was prolonged in 16% of cancer patients.

When prescribing the drugs indicated in the table, it is necessary to monitor the ECG in dynamics: prolongation of the QT interval of more than 25% of the initial value or more than 500 msec is associated with a high risk of pirouette tachycardia. The only exception in this situation is Amiodarone, which almost always leads to an extension of the QT interval, without contributing to the occurrence of VT.

Implantable cardioverters-defibrillators

Implantable cardioverter defibrillators (ICDs) are necessary for primary and secondary prevention of SCD, including ventricular tachyarrhythmias. The data of modern studies have demonstrated a decrease in mortality when using ICD in patients with ischemic and non-ischemic cardiomyopathy as part of the primary prevention of SCD. Indications for implantation of these devices are described in detail in the

recommendations of the American College of Cardiology/ American Heart Association (AHA-ACC) and the European Society of Cardiology (ESC). For the relief of frequent ventricular tachyarrhythmias, ICTs are successfully used in patients with heart neoplasms, such as rhabdomyoma and lipoma. In general, ICD recommendations do not differ for oncological and non-oncological patients, however, there are a number of features [3-8].

Firstly, studies that included patients with cardiomyopathy and the NYHA IV FC heart failure clinic did not demonstrate the benefits of ICD therapy as part of the primary prevention of SCD in mortality.

This category of patients has an extremely unfavorable prognosis and the probability of death from heart failure and comorbid pathology is higher than from ventricular tachyarrhythmias. Similar results can be expected in patients with oncological pathology; even if there are indications for implantation of a cardioverter defibrillator, if the expected life expectancy is less than 1 year, the probability of dying from SCD due to ventricular tachyarrhythmias becomes unlikely. Also, with the terminal stage of the oncological process and a probable life expectancy of more than 1 year, ICDs will practically not affect the quality of life, so they are rarely used in this cohort of patients. Secondly, a number of chemotherapeutic drugs contribute to a decrease in the left ventricular ejection fraction during treatment, which is able to recover in the future (for example, when trastuzumab is prescribed). Potentially reversible causes of LV dysfunction should be evaluated, because in some cases the use of ICD may be justified (for example, if anthracycline therapy was carried out several years ago, and severe progressive left ventricular dysfunction is currently taking place).

Thirdly, the presence of ICD complicates the diagnosis and treatment of cancer patients. A particularly urgent problem in this group of patients is the inability to perform MRI after implantation of the device. But modern technologies allow us to overcome this barrier: implantation of MRI-compatible devices is currently possible. Also, special precautions are necessary when performing electrocoagulation during surgical manipulations, radiation therapy.

Conclusion

Despite the fact that cardiovascular diseases and cancer remain the two most common causes of death, progressive methods of diagnosis and treatment in both areas have significantly reduced mortality from these nosologies. With the use of new therapeutic agents, many malignant neoplasms can be considered as part of a "chronic" process, and the number of cancer survivors continues to grow progressively. However, many chemotherapeutic drugs, radiation therapy can have an adverse effect on the cardiovascular system. In this regard, the problem of cardioncology becomes especially relevant. Initially, attention was focused on cardiomyopathies and heart failure induced by chemotherapy. But it is also necessary to remember about heart rhythm and conduction disorders that may occur in this cohort of patients.

Cardiologists are responsible for identifying a group of patients with a high risk of developing cardiovascular complications even before the start of potentially cardiotoxic chemotherapy. In addition, for the timely adoption of preventive and therapeutic measures, continuous monitoring of cardiac safety in cancer patients receiving chemotherapeutic treatment is necessary.

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