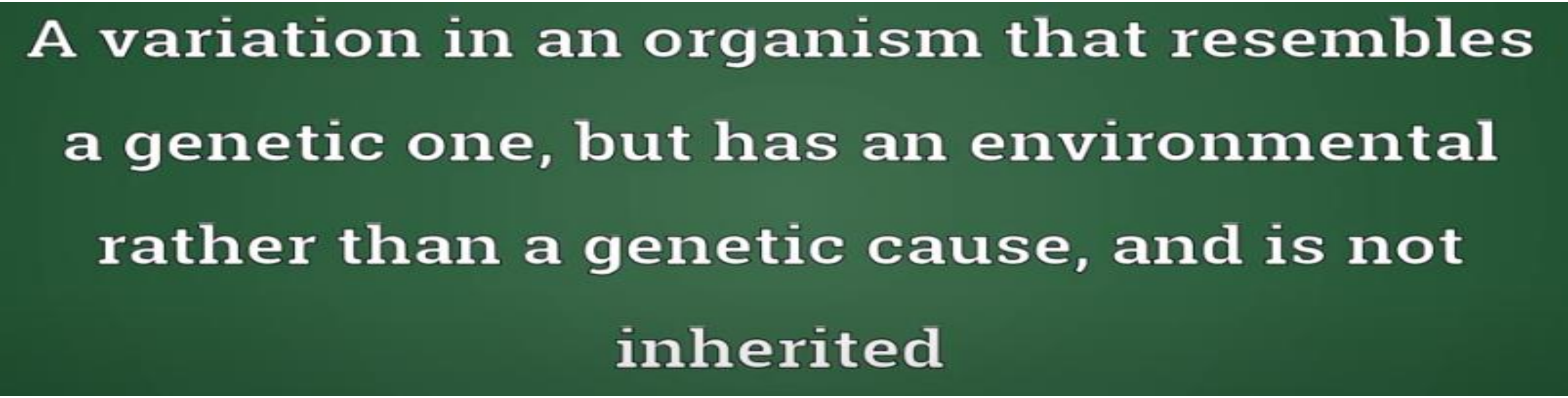
Brugada phenocopies

“ A phenotypic trait or disease that resembles the trait expressed by a particular genotype, but in an individual who is not a carrier of that genotype”.

Phenocopy



The definition of the Brugada syndrome: Point of view

Brugada syndrome (BrS) is a hereditary arrhythmic entity with a low and incomplete worldwide prevalence (0.5 per 1,000 or 5 to 20 per 10,000 individuals), predominant in Southeast Asia (prevalence of 3.7 per 1,000) and in general much more frequent in Asians in relation to other ethnic groups: nine times more common in relation to Caucasians, 36 times more common than in Hispanics and almost non-existent in the north of the African continent Denmark. The entity is also highly prevalent in males (male / female ratio 9: 1 in Southeast Asia and 3: 1 male/female ratio in Caucasians), caused by alterations in the structure and function of certain cardiac ion channels and less expression of connexin 43 (Cx43) in the right ventricle predominantly in ventricular outflow tract (RVOT) causing electromechanical abnormalities. The lower and heterogeneous expression of Cx43 produces functionally significant electrophysiological heterogeneity in the thickness of the ventricular wall and may be a mechanism to promote transmural dispersion of repolarization. Until recently, it was considered an autosomal dominant Mendelian entity in ≈ 25% of cases or sporadic, although it is currently thought to be most likely an oligogenic disorder, rather than a Mendelian condition *, affecting several loci, influenced by environmental factors and whose Diagnosis is based on the presence of a spontaneous or drug-induced coved-type ST segment elevation characterized by elevation of the J point and the ST segment of ≥2 mm, of superior convexity “coved type” (Subtype 1A) or descending rectilinear (Subtype 1A) followed by a symmetric negative T wave in ≥ 1 high right and / or right precordial lead; with (Subtype 1C) or without associated early repolarization pattern in the inferior or inferolateral wall with an increased risk of syncope, (fainting), palpitations, precodial pain, seizures, difficulty breathing(nocturnal agonal respiration), and / or sudden cardiac death (SCD) secondary to polymorphic ventricular tachycardia / ventricular fibrillation (PVT/VF) unexplained cardiac arrest or documented VF/polymorphic VT or paroxysmal atrial fibrillation in the absence of **macroscopic** or **apparent** structural heart disease, electrolyte disturbance, use of certain drugs or coronary heart and fever. and that typically occurs midnight-to-early-morning period at rest (≈80% of cases) or or at a low level of physical activity especially during sleep, which suggests

that the parasympathetic is a determining factor in, arrhythmogenesis: Higher level of vagal tone and higher levels of Ito at the slower heart rates. Although it is considered a genetic disease, its mechanism remains unknown in≈70-75% of cases and a single mutation is not sufficient to cause the BrS phenotype cases. Although ≈20% of patients with BrS carry mutations in *SCN5A*, the molecular mechanisms underlying this condition are still largely unknown.. BrS is associated in with mutations in the SCN5A gene, which encodes for the pore-forming α subunit of the cardiac Na^+ channels. *SCN5A*, which was identified as the first BrS-associated gene in 1998, has emerged as the most common gene associated with BrS, Only the *SCN5A* gene is classified as having definitive evidence as a cause for BrS. The role of genetics in the approach to the arrhythmic patient, progressing beyond the concept of "one mutation, one disease", and raising concerns about the most appropriate approach to patients affected by structural/electrical cardiomyopathy. Currently, the best model is the human patient population and probably BrS is an oligogenic disease **(1)** There have been more than 400 mutations in SCN5A gene that have been associated with BrS. This evidence-based review of genes reported to cause (BrS) and routinely clinically tested in patients indicates that 20 of 21 genes lack sufficient genetic evidence to support their causality for BrS. Type 2 pattern has also been associated with mutations in SCN5A, glycerol-3-phosphate dehydrogenase 1-like (GPD1L), which is the domain responsible for a site homologous to SCN5A, and CACNA1C, the gene responsible for the α-subunit of cardiac L-type calcium channels (LTCC) Mutations of 21 genes other than SCN5A have been implicated in the pathogenesis of BrS to date. Multiple pathogenic variants of genes have been shown to alter the normal function of Na+, K^+ Gain-of-function mutations in genes encoding for potassium channels have also been implicated in BrS. Genes influencing Ito include KCNE3, KCND3 and SEMA3A (semaphoring, an endogenous K+ channel inhibitor) while KCNJ8 and ABCC9 (encoding for SUR2A, the ATP-binding cassette transporter for the KATP channel) mutations affected the IK,ATP. .

1. **Michelle M. et al.Brugada Syndrome: Oligogenic or Mendelian Disease? Int J Mol Sci. 2020 Mar; 21(5): 1687.Published online 2020 Mar 1. doi: 10.3390/ijms21051687**

KCNH2, which encodes for IKr was proposed by Wang et al.(1) to be involved in BrS development.
Dysfunction in the KCNAB2, which encodes the voltage-gated K^+ channel β2-subunit, was associated with increased Ito activity and identified as a putative gene involved in BrS. Kvβ2 dysfunction can contribute to the Brugada electrocardiographic pattern.(2)

Classification of hereditary diseases

- ***Monogenic or Mendelian,*** to be transmitted to the offspring according to Mendel's laws. They can be
    1. Autosomal Dominant,
    2. Autosomal Recessive, or
    3. X-linked.

    Mendelian inheritance refers to the patterns of inheritance that are characteristic of organisms that reproduce sexually. It refers to the type of inheritance that can be easily understood as a consequence of a single gene.
- ***Multifactorial or polygenic:*** produced by mutations in several genes, generally of different chromosomes and the combination of multiple environmental factors (age, sex, bad habits (obesity, tobacco, alcohol), toxic environments or a limited childhood.) And
- ***Polygenic Oligogenic*,*** where there are a few genes that have more influence than the rest. In the case of BrS, the SCN5A gene and that depending on its presence other mutations are expressed (epistasis: https://academic.oup.com/hmg/article/11/20/2463/616080). Despite their importance, mutations in the SCN5A gene are present in ≈20 to 30% of cases.

1. **Q Wang 1, Seiko Ohno , Wei-Guang Ding , Megumi Fukuyama , Akashi Miyamoto, Hideki Itoh , Takeru Makiyama ,et al Gain-of-Function KCNH2 Mutations in Patients with Brugada Syndrome. J Cardiovasc Electrophysiol . 2014 May;25(5):522-530. doi: 10.1111/jce.12361.**
2. **Vincent Portero, Solena Le Scouarnec, Zeineb Es-Salah-Lamoureux, Sophie Burel, Jean-Baptiste Gourraud, Stéphanie Bonnaud, Pierre Lindenbaum, et al. Dysfunction of the Voltage-Gated K+ Channel β2 Subunit in a Familial Case of Brugada Syndrome,J Am Heart Assoc. 2016 Jun; 5(6): e003122. doi: 10.1161/JAHA.115.003122**

Brugada syndrome diagnosis criteria from first and second consensus 2005 (4;5)

BrS is diagnosed in patients with ST-segment elevation with type 1 morphology ≥2 mm in ≥1 lead among the right precordial leads V1, V2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs. 2. BrS is diagnosed in patients with type 2 or type 3 ST-segment elevation in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology in

1) ***Absence of apparent structural heart disease,***
2) ***Absence of drugs effects, electrolyte disturbance and coronary artery disease,***
3) ***Documented PVT/VF***
4) ***Family history of SCD at <45 years in first-degree relatives(SCD is commonly defined as death from an unexpected circulatory arrest, occurring within an hour of the onset of symptoms. Unexplained SCD is defined as no apparent structural or electrical heart disease after extensive investigations. When VF has been documented by electrocardiography during resuscitation maneuvers, unexplained SCD is termed as Idiopatic VF. (1;2;3.)***
5) ***Type 1 ECG Brugada pattern (coved-type) in proband and family members,***
6) ***Induction of VT/VF with Programmed Electrical Stimulation,***
7) ***Syncope, cardiac arrest or nocturnal agonal respiration.***

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2013) HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes (1)

Both previous consensus documents (**1;2**) stated that the definitive diagnosis of BrS should only be established when the type I ECG pattern is documented in combination with at least one of the following clinical criteria: documented ventricular fibrillation (VF), documented polymorphic ventricular tachycardia (VT), inducible ventricular arrhythmias during electrophysiological study (EPS), syncope or nocturnal agonal respiration, a family history of SCD at <45 years of age, or type I ECG pattern in other family members. ***Currently a type I ECG pattern alone, even when other clinical criteria are not fulfilled, can be associated with SCD during follow-up.[12] Thus, all patients who present a type I ECG pattern, even when isolated, should be considered at risk.***

1. **Wilde AA.M, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al.. Proposed diagnostic criteria for the Brugada syndrome.. Eur Heart J, 23 (2002), pp. 1648-54**
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3. **Priori S.G., Wilde A.A., Horie M., et al. (2013) HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 10:1932–1963. DOI: 10.1016/j.hrthm.2013.05.014**

Number of electrocardiogram leads in the diagnosis of spontaneous Brugada syndrome.

The recently recommended single lead-based criterion for the diagnosis of BrS may lead to overdiagnosis of this disorder and overestimation of the risk of SCD. To investigate the value of a single-lead diagnosis in patients with BrS and a spontaneous type 1 pattern, Arnaud et al studied consecutive patients with BrS included in a multicenter prospective registry; only those with a spontaneous type 1 ECG were enrolled. Clinical and ECG data were reviewed by two physicians blinded to the patients' clinical and genetic status. Among 1613 patients, 505 (31%) were enrolled (79% male; mean age 46±15 years). A spontaneous type ECG pattern was found in one lead in 250 patients (**group 1**), in two leads in 227 patients (**group 2**) and in three leads in 27 patients (**group 3**).

Groups were similar except for individuals in group 3, who presented more frequently a fQRS complex, ERP and a prolonged T_{peak}-T_{end} interval. After a mean follow-up of **6.4±4.7 years**, ventricular arrhythmia, SCD or ICD shock occurred in 46 (9%) patients, without differences between groups. They concluded that the prognosis of BrS with a spontaneous type 1 ECG pattern does not appear to be affected by the number of leads required for the diagnosis.

1. **Marine Arnaud, Pauline Berthome, Romain Tixier, Jean Briand, Olivier Geoffroy, Xavier Le Guillou, Dominique Babuty, Jacques Mansourati, Laurence Jesel, Jean-Marc Dupuis, Paul Bru, Florence Kyndt, Béatrice Guyomarch, Aurélie Thollet, Nathalie Behar, Philippe Mabo , Frédéric Sacher, Vincent Probst, Jean-Baptiste Gourraud Number of electrocardiogram leads in the diagnosis of spontaneous Brugada syndrome. Arch Cardiovasc Dis. 2020 Mar;113(3):152-158. doi: 10.1016/j.acvd.2019.10.007.**

Variations to Mendel´s Laws Extensions and Exceptions

In these cases, genotypic ratio is a Mendel predicted but phenotypic ratio is altered

1) **Lethal allele combinations** A pair of identical alleles that are both present in an organism that ultimately results in death of that organism are referred to as recessive lethal alleles. Though recessive lethals may code for dominant or recessive traits, they are only fatal in the homozygous condition. Examples of diseases caused by recessive lethal alleles are cystic fibrosis, Tay-Sachs disease, sickle-cell anemia, and **brachydactyly.**
2) **Multiple alleles:** Today, we know that not all alleles behave quite as straightforwardly as in Mendel's experiments. For example, in real life: Allele pairs may have a variety of dominance relationships (that is, one allele of the pair may not completely "hide" the other in the heterozygote).There are often many different alleles of a gene in a population.
3) **Different dominance relationships** Dominance is a relationship between two alleles of a gene and their associated phenotypes. A "dominant" allele is dominant to a particular allele of the same gene that can be inferred from the context, but it may be recessive to a third allele, and codominant to a fourth.
4) **Epistasis** is a phenomenon in genetics in which the effect of a gene mutation is dependent on the presence or absence of mutations in one or more other genes, respectively termed modifier genes. In other words, the effect of the mutation is dependent on the genetic background in which it appears. Epistatic mutations therefore have different effects on their own than when they occur together. Originally, the term *epistasis* specifically meant that the effect of a gene variant is masked by that of a different gene.

1) **Penetrance and expressivity:** is used to describe whether or not there is a clinical expression of the genotype in the individual. Expressivity is the term that describes the differences observed in the clinical phenotype between two individuals with the same genotype.

2) **Pleiotropy** occurs when one gene influences two or more seemingly unrelated phenotypic traits. Such a gene that exhibits multiple phenotypic expression is called a pleiotropic gene. Mutation in a pleiotropic gene may have an effect on several traits simultaneously, due to the gene coding for a product used by a myriad of cells or different targets that have the same signaling function.

3) **Genetic heterogeneity:** Genetic heterogeneity occurs through the production of single or similar phenotypes through different genetic mechanisms. There are two types of genetic heterogeneity: allelic heterogeneity, which occurs when a similar phenotype is produced by different alleles within the same gene; and locus heterogeneity, which occurs when a similar phenotype is produced by mutations at different loci

4) **Phenocopies** The term was coined by Richard Goldschmidt in 1935. He used it to refer to forms, produced by some experimental procedure, whose appearance duplicates or copies the phenotype of some mutant or combination of mutants. A phenotypic trait or disease that resembles the trait expressed by a particular genotype, but in an individual who is not a carrier of that genotype

Definition and Diagnostic Criteria for Brugada Phenocopy Source Dr Baranchuk

Brugada Phenocopies(BrPs) are clinical entities characterized by Brugada ECG pattern type I and type II in the absence of BrS. A phenotypic trait or disease that resembles the trait expressed by a particular genotype, but in an individual who is not a carrier of that genotype. an environmentally induced, nongenetic alteration of a phenotype to a form that resembles the expression of a known genetic mutation.

Diagnostic criteria for BrP are:

- Characteristic type I or type II Brugada ECG pattern
- The presence of an underlying condition inducing Brugada ECG patterns
- Resolution of the ECG patterns after eliminating the underlying condition
- Low pretest probability for BrS as defined by lack of clinical symptoms, medical history and family history suggestive of BrS
- Negative provocative testing with sodium channel blocker drugs (not mandatory if surgical RVOT manipulation has occurred within the last 96 hours)
- A negative genetic testing for SCN5A (recommended but not mandatory as it is possible to identify mutation only in 20%-30% of probands that are known to have BrS.

Diagnostic criteria for Brugada phenocopy (First 4 criteria are mandatory)

1. ECG pattern has type 1 or type 2 Brugada morphologic criteria
2. Presence of an underlying condition that is identifiable and reversible
3. Resolution of the ECG pattern upon elimination of the underlying condition
4. Low pretest probability for Brugada syndrome determined by the lack of symptoms, clinical history, and family history
5. A negative provocative test with a sodium channel blocker drug (e.g., ajmaline, flecainide, or procainamide)*
6. A negative genetic test**

*Provocative testing is not mandatory if surgical right ventricular outflow tract manipulation has occurred within the last 96 hours.

**Desirable, but not mandatory, since the SCN5A mutation has been identified in only 20-30% of probands affected by Brugada syndrome.

ECG: Electrocardiogram.

The characteristic ST-segment elevation seen in BrPs can be explained by a transmural gradient that arises from an accentuated I_{to}-mediated action potential notch and a loss of the AP dome in the epicardium but not the endocardium. The loss of the AP dome can result from a disruption in the homeostasis of active inward and outward currents at the end of phase 1 of the AP.Specifically, any mechanism that increases (↑) outward, I_{to},, adenosine triphosphate-sensitive potassium current ($I_{K\text{-}ATP}$), delayed rectifier potassium current [I_{Ks},I_{Kr}]) or decreases outwards currents (i.e., $I_{Ca\text{-}L}$, fast I_{Na}) will result in the characteristic ST-segment elevation seen in the Brugada Type-1 ECG. This provides a possible explanation of the general, underlying pathogenesis of the diverse forms of BrPs. (Shimizu W. Acquired forms of the Brugada syndrome. *J Electrocardiol* 2005;38:22–25.)

Morphologic classification system for Brugada phenocopy Dr BARANCHUK

Type	
Type 1	BrP with a coved Brugada ECG pattern
Type 2	BrP with a saddleback Brugada ECG pattern
Class	
Class A	All mandatory BrP diagnostic criteria are satisfied, including positive results from a provocative drug challenge with sodium channel blockers
Class B	Highly suspected BrP: Not all mandatory criteria are complete*
Class C	Highly suspected BrP: Provocative drug challenge is not indicated and/or justified**

*This group includes cases in which a provocative drug challenge is pending or it is not possible to perform due to various factors, such as the patient is lost to follow-up or deceased.

**This group includes cases in which a provocative drug challenge is not clinically indicated, such as patients with recent surgical right ventricular outflow tract manipulation or BrP secondary to the use of inappropriate high-pass ECG filtering. BrP: Brugada phenocopy; ECG: Electrocardiogram.

Etiologic classification for Brugada phenocopy

1. **Metabolic conditions: Hyperkalemia and severe hypokalemia due to gastrointestinal loss.(1;2;3),** hyponatremia, hypercalcemia, hypothermia
2. **Mechanical compression** with involvement of the RVOT by either mediastinal mass, intracardiac tumors or metastatic carcinomas. **.(4)**
3. **Ischemia and pulmonary embolism** ischemia-induced transient ion channel dysfunction generating ↑Ito current and decreased ↓Na+.(5)
4. **Myocardial and pericardial disease:** Chagas myopathy,**(6;7)** acute and chronic myocarditis,(8) acute pericarditis(9)
5. **Electrocardiogram modulation**
6. **Miscellaneous:** consumption of yellow oleander seeds (T. Peruviana). (10) Methanol Intoxication (11)

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ECG modulation

Another underlying condition for BrP is the improper application of high-pass filtering. Normally a high- -pass filter is used for eliminating low frequency noises during ECG recording which are most likely resulted from movement of ECG electrodes on the skin, physicochemical skin-electrode changes and body movement related to normal breathing. Low frequency components of normal ECG such as ST segment can be distorted in case applying non-recommended cutoff frequency values. Importantly, although the change in the ST segment by applying improper high-pass filter depends on the baseline ECG characteristics, it is more common in the right precordial leads. whom application of a nonstandard high-pass filter of 0.5 Hz produced Brugada ECG pattern. **(1)**

Miscellaneous

BrP in patients with Ebstein anomaly, **(2)**intracranial hemorrhage**(3)** and following biphasic synchronized electrical cardioversion for atrial fibrillation. **(4)**

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3. **Abdalla KA, Sorgente A, Brugada P. Transient appearance of Brugada-like Type 1 electrocardiogram pattern immediately after biphasic synchronized electrical cardioversion for atrial fibrillation: a case series. European Heart Journal-Case Reports 2019;1–8.**

Recommendations for future Brugada phenocopy case report publication(1)

1. **It is mandatory to include a 12-lead ECG tracing with emphasis on the right precordial leads V_1–V_3.**
2. **The inclusion of additional leads is desirable and highly recommendable.(2)**
3. **It is paramount to comment on the presence of a past medical history of syncope and a family history of sudden death or syncope, which can be of help in differentiating between BrS from BrPs. Including whether or not provocative testing, genetic testing**
4. **To preform an ECG tracings of immediate family members were recorded is also important in helping to rule out true BrS.**
5. **To report whether the Brugada ECG pattern resolved after the treatment of the underlying cause; otherwise it is difficult to classify them as a BrP, because we cannot know whether the underlying condition was truly behind the Brugada ECG manifestation.**
6. **It is important to document the resolution of the Brugada ECG to infer a direct association between the "environmental factor" and the Brugada ECG pattern.**
7. **The transient nature of the ECG alteration is a hallmark in differentiating Brugada syndrome from Brugada phenocopy(3)**

1. *Es obligatorio incluir un trazado de ECG de 12 derivaciones con énfasis en las derivaciones precordiales correctas V1 - V3.*
2. *La inclusión de derivaciones adicionales es deseable y muy recomendable. (2)*
3. *Es fundamental interogar sobre la presencia de antecedentes de síncope y antecedentes familiares de muerte súbita o síncope, que pueden ser de ayuda para diferenciar entre SBr y BrP. Incluyendo pruebas de provocación o no, pruebas genéticas*
4. *Para realizar un ECG, se realizaran los trazados de los familiares directos importante para ayudar a descartar un verdadero SBr.*
5. *Informar si el patrón ECG de Brugada se resolvió después del tratamiento de la causa subyacente; de lo contrario, es difícil clasificarlos como BrP, porque no podemos saber si la condición subyacente estaba realmente detrás de la manifestación del ECG de Brugada.*
6. *Es importante documentar la resolución del ECG de Brugada para inferir una asociación directa entre el "factor ambiental" y el patrón del ECG de Brugada.*
7. *Cuando el patrón electrocardiográfico es transitorio es indicativo de que se trata de BrS y no de BrP;*

1. **Adrian Baranchuk 1, Timothy Nguyen, Min Hyung Ryu, Francisco Femenía, Wojciech Zareba, Arthur A M Wilde, Wataru Shimizu, Pedro Brugada, Andrés R Pérez-Riera. Brugada phenocopy: new terminology and proposed classification, Ann Noninvasive Electrocardiol. 2012 Oct;17(4):299-314. doi: 10.1111/j.1542-474X.2012.00525.x.**
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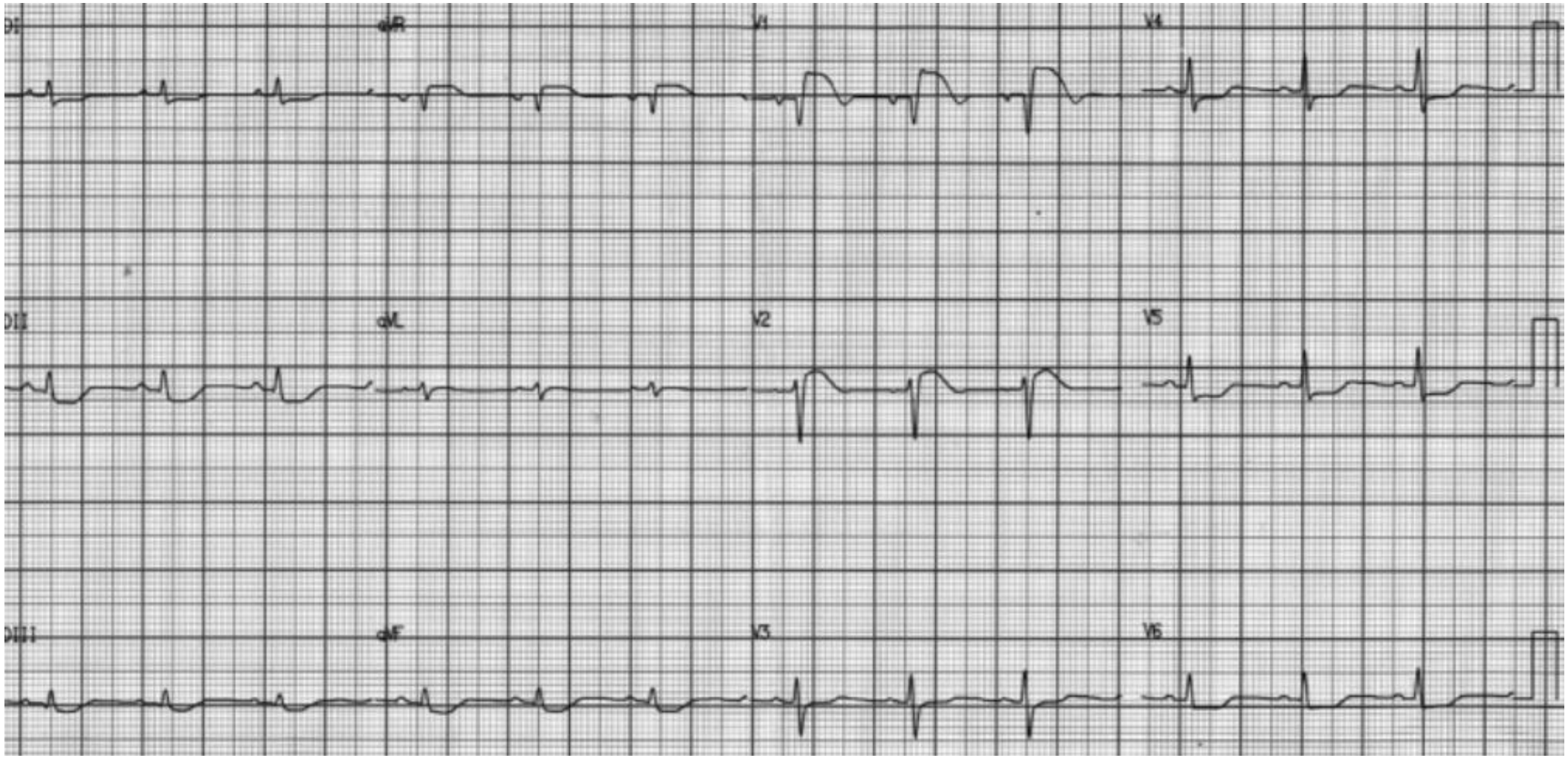
Using simulations of the anterior ventricular wall Rivera –Juarez et al. showed that potassium concentration, fibrosis, and I_{to} are all involved the development of the Brugada pattern and act synergistically to shape the characteristic pattern (**Rivera-Juárez A, Hernández-Romero I, Puertas C, et al. Clinical characteristics and electrophysiological mechanisms underlying Brugada ECG in patients with severe hyperkalemia. J Am Heart Assoc. 2019;8(3):e010115.)**

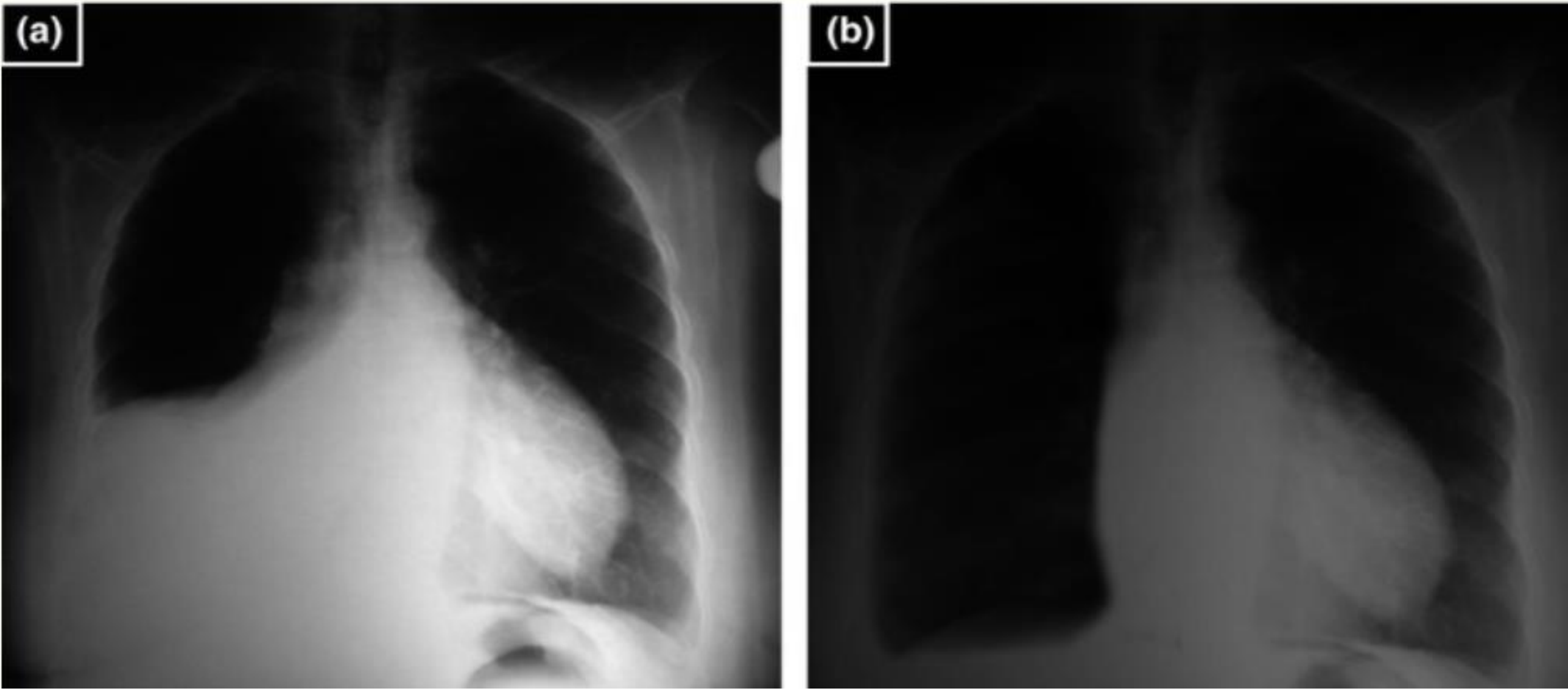
Brugada phenocopy caused by a compressive mediastinal tumor.

We presented a case of mediastinal non-Hodgkin's lymphoma that compressed the RVOT originating a type 1 Brugada ECG pattern. After the treatment and lymphoma reversal, this pattern disappeared. The negative provocative ajmaline test indicates low probability of Brugada syndrome.

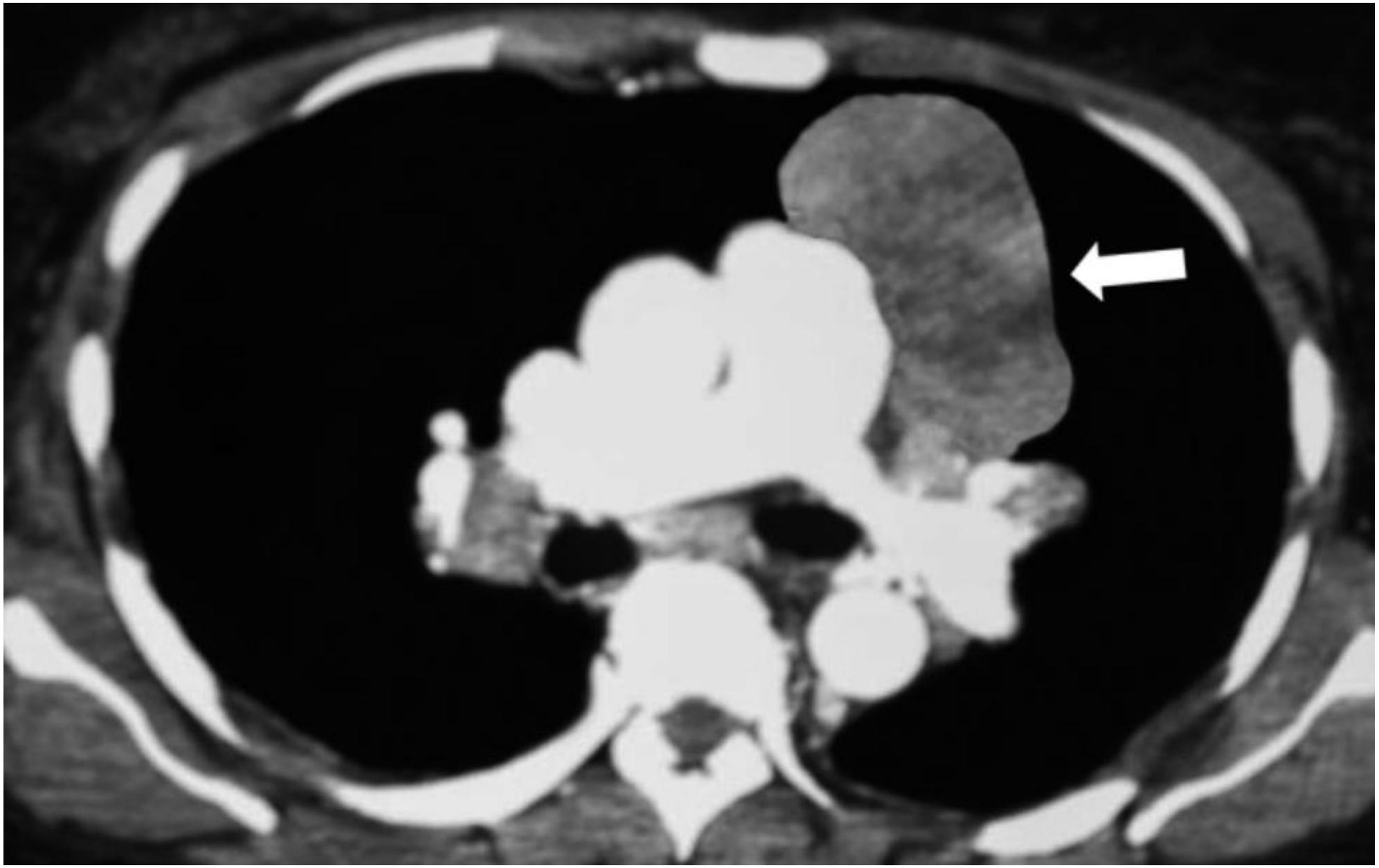


Initial ECG. STE in aVR and from V_1–V_3 decreasing progressively (this characteristic differentiates RV infarction from anteroseptal LV infarction). Concomitantly, ST depression is observed in inferior and lateral walls. Conclusion: type 1 Brugada ECG pattern

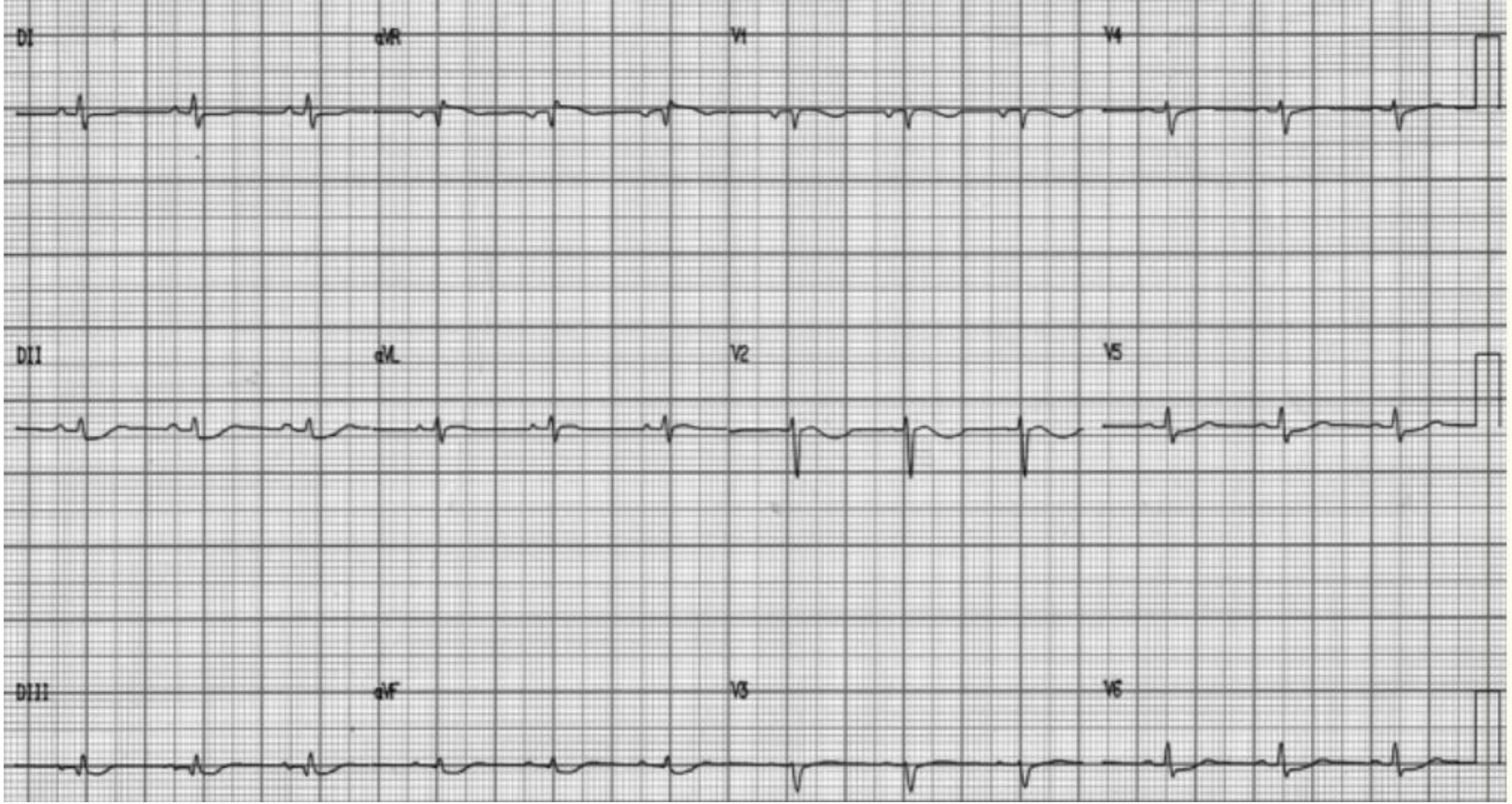
Posteroanterior chest x-ray showed a large pleural effusion on the right side that disappeared after treatment.



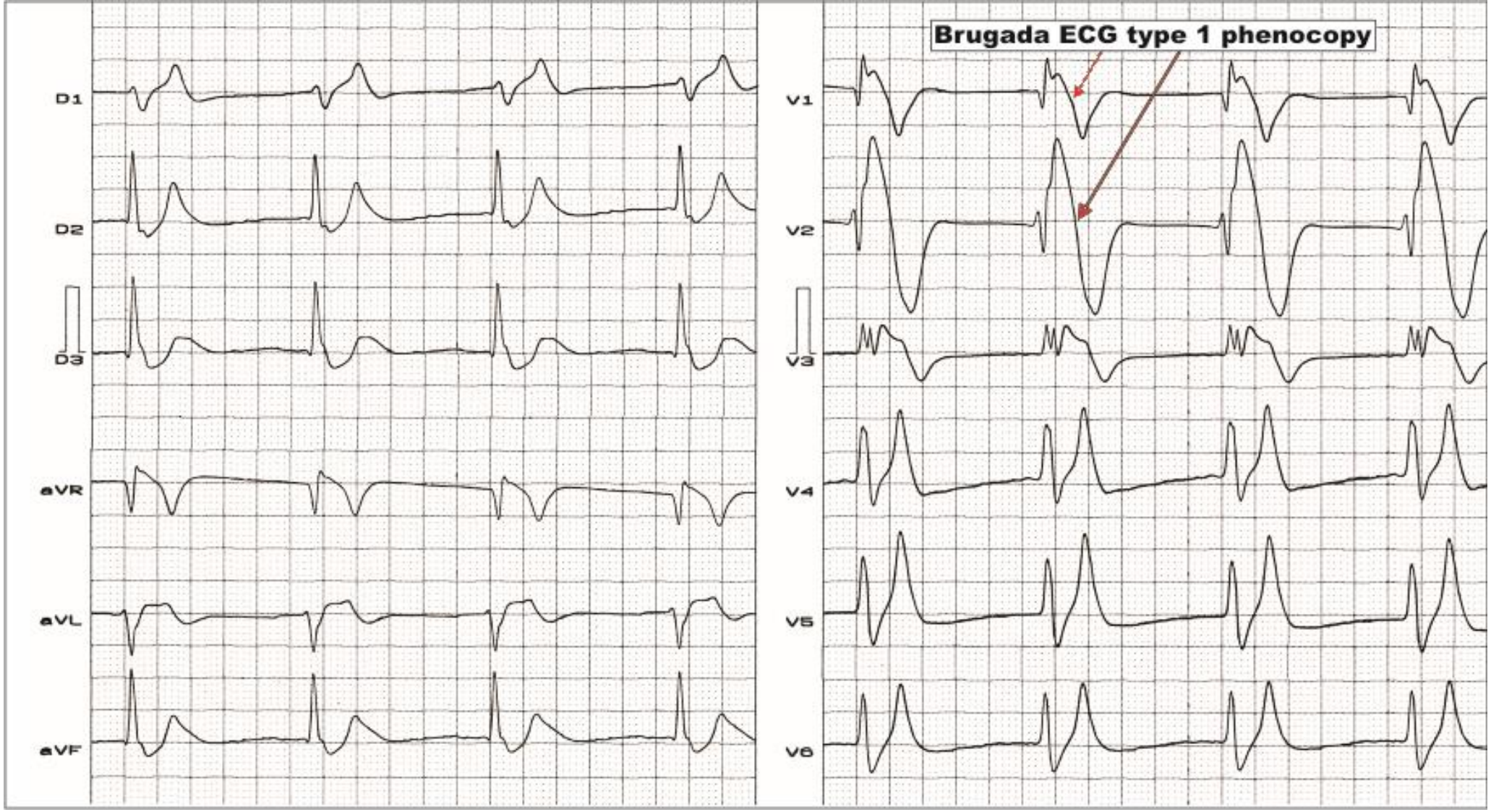
Posteroanterior chest x-ray. Large pleural effusion before (a) and after treatment (b)



The computed tomography indicates the tumor extension (arrow)

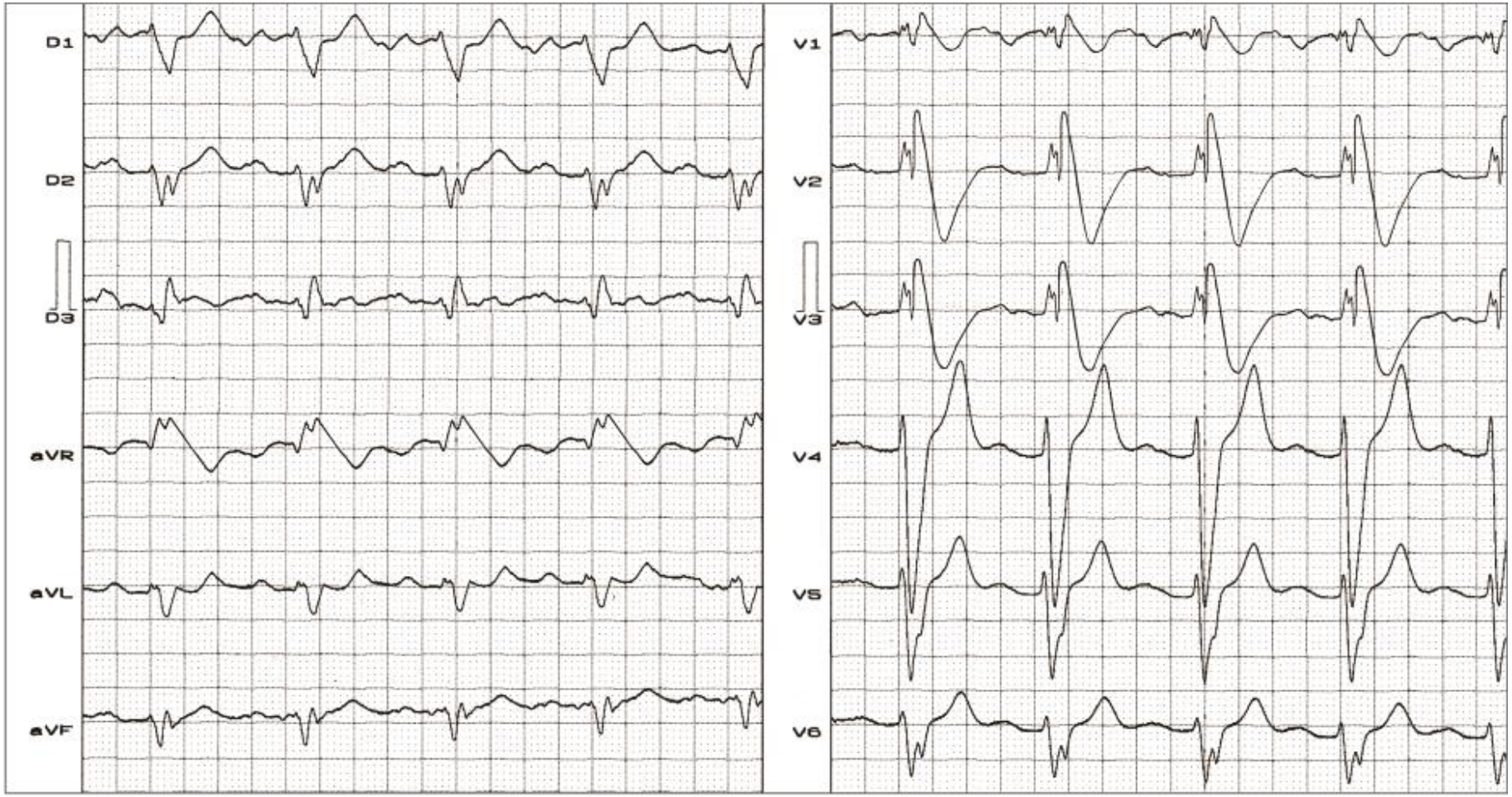


ECG normalization after oncologic therapy. Low QRS voltage in the limb leads (<5 mm) and precordial leads (<10 mm), ST depression in inferior and lateral precordial leads



Clinical diagnosis: terminal renal insufficiency. Severe hyperkalemia: K^+ 8.7 mEq/L. This sign is known as dialyzable injury current. ECG diagnosis: very likely, junctional with P waves near J point, HR: 54 bpm, QRSd: 160 ms, ST segment elevation from V_1 to V_3 and I, aVL and aVR. V_1 to V_3 display ST segment upwardly convex pattern, similar to Brugada syndrome or Brugada phenocopy", typical T waves in "tent", pointed, and with a narrow base.

Next figure shows a Brugada phenocopy secondary to accidental plasma concentrations of propafenone in the toxic range.



ECG diagnosis: Left atrial enlargement, PR interval prolongation or first-degree AV block secondary to augmentation of effective refractory periods of atrioventricular node (> AH interval), His-Purkinje system (> HV interval), nonspecific intraventricular conduction disturbance, (marked abnormal ventricular activation pattern (bizarre): does not satisfy the criteria of either LBBB or RBBB), long QT interval with normal JT interval and Brugada type 1 ECG phenocopy: ST segment elevation convex to the top followed by negative T waves from V_1 to V_3 Induced Brugada-type 1 ECG pattern, is a sign for imminent malignant arrhythmias.

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