Concomitant presence of *JAK2*V617F mutation and *BCR-ABL* translocation in two patients: A new entity or a variant of myeloproliferative neoplasms (Case report)

FILIPA MOUSINHO[1*], ANA P. AZEVEDO[2-4*], TATIANA MENDES[1], PAULA SOUSA E SANTOS[1], RITA CERQUEIRA[5], SÓNIA MATOS[6], SÓNIA SANTOS[6], SÂNCIA RAMOS[7], JOÃO FARO VIANA[2] and FERNANDO LIMA[1]

Departments of [1]Clinical Hematology and [2]Clinical Pathology, Hospital of São Francisco Xavier, West Lisbon Hospital Centre, 1449-005 Lisbon; [3]Centre for Toxicogenomics and Human Health (ToxOmics), Genetics, Oncology and Human Toxicology, NOVA Medical School/Faculty of Medical Sciences, NOVA University of Lisbon, 1169-056 Lisbon; [4]Superior Institute of Health Sciences Egas Moniz, 2829-511 Monte da Caparica; [5]CGC Clinical Genetics Centre, 4000-432 Porto; [6]GenoMed-Molecular Medicine Diagnosis, Molecular Medicine Institute, Faculty of Medicine University of Lisbon, 1649-028 Lisbon; [7]Pathology Department, Hospital of São Francisco Xavier, West Lisbon Hospital Centre, 1449-005 Lisbon, Portugal

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Abstract. Myeloproliferative neoplasms (MPNs) are classically divided into BCR RhoGEF and GTPase activating protein (*BCR*)-ABL proto-oncogene 1 non-receptor tyrosine kinase (*ABL*) positive chronic myeloid leukemia (CML) and BCR-ABL negative MPNs, including essential thrombocythemia (ET). One of the major diagnostic criteria for ET is the absence of the philadelphia chromosome, thus when present it is almost indicative of CML. ET and CML are considered to be mutually exclusive; however, there are rare situations in which patients with ET present positive *BCR-ABL* without the features of CML. Although from the literature review, the frequency of *JAK2*V617F mutation and *BCR-ABL* translocation coexistence in MPNs is low, it may be higher than expected. The current study reported cases of two patients with an initial diagnosis of ET in the presence of *JAK2*V617F mutation and *BCR-ABL* translocation by fluorescent *in situ* hybridization. Both patients presented with a heterozygous *BCR-ABL* translocation, and absence of p190 and p210 transcripts, seemingly a der(9) in the background of an ET *JAK2*V617F mutation.

Correspondence to: Dr Ana P. Azevedo, Department of Clinical Pathology, Hospital of São Francisco Xavier, West Lisbon Hospital Centre, Estrada do Forte do Alto do Duque, 1449-005 Lisbon, Portugal
E-mail: anpazevedo@gmail.com

*Contributed equally

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Introduction

According to World Health Organization (WHO) 2008 Classification of tumours of haematopoietic and lymphoid tissues and 2016 revision, myeloproliferative neoplasms (MPNs) can be classified into two major groups, chronic myeloid leukemia (CML) and Philadelphia-negative MPNs (PN-MPNs), such as polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) (1). These disorders are more frequently found in elderly patients, mostly in men (1).

One of the major genetic insights into the pathogenesis of the PN-MPNs included the identification of the somatic point gain-of-function mutations in Janus kinase 2 gene (*JAK2*), leading to the activation of the JAK/STAT signaling pathway (signal transducer and activator of transcription), culminating in exacerbated cellular proliferation, resistance to apoptosis and evolution to MPNs (2-4). On the other hand, the identification of Philadelphia chromosome (Ph), a translocation involving chromosomes 9 and 22 that results in the formation of the *BCR-ABL* fusion gene, constitutes the defining leukemogenic event in CML (5,6). ET is characterized by a high platelet count, often associated with thrombotic and hemorrhagic events, and the presence of *JAK2* mutation in about 50-60% of cases (7-9).

As far as we know from literature revision, the frequency of concurrent presence of *JAK2*V617F mutation and *BCR-ABL* translocation in a single individual with a MPN is a rare event, independently of what phenotype expresses earlier, PN-MPN or CML (10-13).

Although ET and CML are considered to be mutually exclusive, rare cases of concomitant presence of *BCR-ABL* translocation positive CML and *JAK2*V617F mutation positive ET have been reported in the literature (10,13).

We report here the case of two patients initially included in a data base population of 58 patients with the diagnosis of ET in the presence of *JAK2*V617F mutation, with the suspicion of coexistence with *BCR-ABL* translocation. Patient anonymity was guaranteed and consent was provided, in agreement with the Declaration of Helsinki. The Institutional Ethics Board of the Hospital of São Francisco Xavier, West Lisbon Hospital Centre (Lisbon, Portugal) approved the present study.

Case report

Case report 1. A 75-year-old man with a medical history of dyslipidemia, hypertension, acute myocardial infarction, and ischemic stroke in August 2013. In December 2013 this patient was hospitalized with his second ischemic stroke. Although he had confirmed poor adherence to the prescribed therapy for cardiovascular risk patients, in January 2014 he was referred to the hematology consultation for maintained thrombocytosis and leukocytosis, since at least August 2013 (as there was no previous laboratory data available).

Evaluation revealed platelet count of 1,405x10^9/l, leukocytosis (15x10^9/l), with normal formula, and without immature precursor cells as well as normal hemoglobin (Table I).

Abdominal ultrasound confirmed absent splenomegaly and Bone marrow (BM) aspirate showed megakaryocytic hyperplasia and enlarged megakaryocytes, with no abnormalities of the myeloid and erythroid series (Fig. 1). BM biopsy showed a hypercellular marrow (80%), megakaryocytic and granulocytic (slight) hyperplasia (Fig. 2).

Molecular biology (Fig. 3) and cytogenetic tests were performed in peripheral blood and the results revealed positivity for the *JAK2*V617F mutation and a karyotype of 45,X,-Y[5]/46,XY[15]. The fluorescence *in situ* hybridization (FISH) was positive for the *BCR-ABL* translocation in 16% with an atypical pattern. The *BCR-ABL* transcript was not detected by the conventional reverse transcriptase-polymerase chain reaction (RT-PCR) method (specific for p190 and p210 transcripts). This high risk patient received a daily hydroxyurea (HU), and low dose aspirin regimen as secondary thrombotic prevention. A good response to treatment was achieved, with normalization of leukocytes and platelets reduction of greater than 50% after one month and normalization of platelets after five months of therapy (Table I). This patient had very poor compliance to the therapy and hospital check-ups, so tyrosine kinase inhibitor (TKI) that was planned to be introduced, was never started since the patient did not come to collect the medication at the hospital. His clinical and laboratory situation has worsened and the patient died by the beginning of 2017, from infectious complications.

Case report 2. A 76 years old man, with previous history of cardiovascular risk factors, namely Diabetes mellitus, dyslipidemia and Ischemic cardiomiopathy submitted to cardiac bypass due to myocardial infarction in 2001.

Presented with isolated thrombocytosis (1,022x10^9/l) in 2005, which led the patient to the Hematology Department to study the etiology behind the maintained increased level of platelet count (Table II).

In a patient with previous history of thrombotic event, it was imperative to understand the etiology of such abnormal changes in blood analysis, since it might have been in close relation to the previous cardiac event described.

At this time, high platelet count was asymptomatic, and there was neither clinical nor analytical blood data for detecting an associated inflammatory process or any recent surgeries explaining this finding.

Abdominal ultrasound showed normal spleen morphology, and there were no Howell-Jolly bodies nor pitted erythrocytes found in blood smear analysis, that could be interpreted as reactive thrombocytosis due to functional hyposplenism.

Blood sideremia and iron stores were between normal ranges, and no history of hemorrhage was present. Excluded secondary causes of thrombocytosis and based on an indolent clinical course, a primary cause was admitted. The MPNs are the most common responsible entities and so cytogenetics and molecular biology tests on *JAK2*V617F mutation and *BCR-ABL* t(9;22) were performed in peripheral blood. *JAK2*V617F was positive and, once again, the FISH test was positive for the *BCR-ABL* translocation in 17% with an atypical pattern (Fig. 4), but *BCR-ABL* transcript was not detected by the RT-PCR method. No metaphases were observed in the karyotype for evaluation. Having this data discussed, and taking into account the presence of these mutations, the diagnosis of ET *JAK2*V617F and *BCR-ABL* positive was admitted. The patient started on HU 500 mg (alternate day progressing to 1 g/alternate day) and TKI (Imatinib, 400 mg/day). A few months later, TKI was suspended and the patient remained under treatment with HU, actually with well controlled disease.

Regarding the methodology used for genetic study, extraction of whole DNA from peripheral blood was accomplished by cell lysis followed by ethanol precipitation and recovery of the DNA by elution in a buffer solution (QIAamp® DNA Mini kit; Qiagen GmbH, Hilden, Germany). The presence/absence of *JAK2*V617F mutation was determined by amplification refractory mutation system (ARMS)-PCR (in-house), based on amplification of a genomic fragment which includes the region corresponding to amino acid 617 of the JAK2 protein, and on the differential detection on agarose gel of the normal or mutated alleles through the use of allele-specific primers. The test result is qualitative and the test sensitivity is 1%. Quantification of *JAK2* was obtained by high resolution melting PCR (HRM-PCR) (LightCycler® 480 Instrument; Roche Molecular Diagnostics, Pleasanton, CA, USA), with a sensitivity of about 10% of mutated cells. Conventional RT-PCR was performed for the identification of *BCR-ABL* transcripts (specific for p190 and p210), after RNA extraction, according to the methodology described by van Dongen *et al* (14). Results are analyzed on agarose gel electrophoresis. FISH analysis was done on 100 nuclei after hybridization with specific probes for t(9;22) *BCR-ABL* (Vysis LSI *BCR-ABL* Dual Color, Dual Fusion Translocation Probe).

Discussion

Several authors have investigated the relationship between *JAK2*V617F and *BCR-ABL* anomalies and many theories have been postulated in the last years, especially after the identification of *JAK2*V617F mutation in 2005.

Table I. Results over time and therapy prescribed for case study 1.

	Time point					
	2014				2016	2017
Characteristic	January	February	June	September	August	January
Platelets (x10^9/l)	1,405	698	375	547	199	1,596
Hemoglobin (g/dl)	14.3	13.4	12.3	12.8	13.9	7.9
Leucocytes (x10^9/l)	15.1	6.9	6.2	6.3	3.9	18.9
JAK2V617F mutation	Positive (25%)	-	-		Positive	-
BCR/ABL t(9;22) (FISH)	Positive 16% (atypical pattern)	-	-	Positive 21% (atypical pattern)	-	-

Hydroxyurea and aspirin were given from January 2014 onwards. Due to maintained thrombocytosis and leukocytosis, and thrombotic previous history, patients received a daily hydroxyurea and low dose aspirin therapeutic regimen. *BCR/ABL*, BCR RhoGEF and GTPase activating protein-ABL proto-oncogene 1 non-receptor tyrosine kinase; FISH, fluorescent *in situ* hybridization.

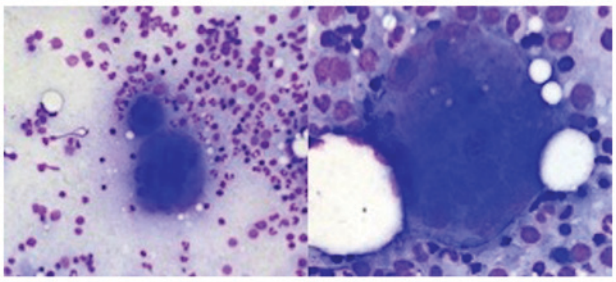

Figure 1. Case study 1: Bone marrow aspirate showed megakaryocytic hyperplasia and enlarged megakaryocytes, with no abnormalities of the myeloid and erythroid series (May-Grünwald-Giemsa stain, x40 and x100).

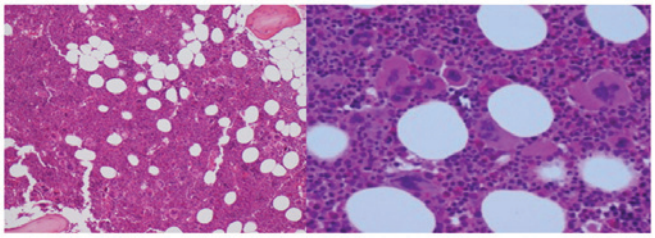

Figure 2. Case study 1: Bone marrow biopsy showed a hypercellular marrow (80%), megakaryocytic and granulocytic hyperplasia (hematoxylin and eosin staining, x40 and x100).

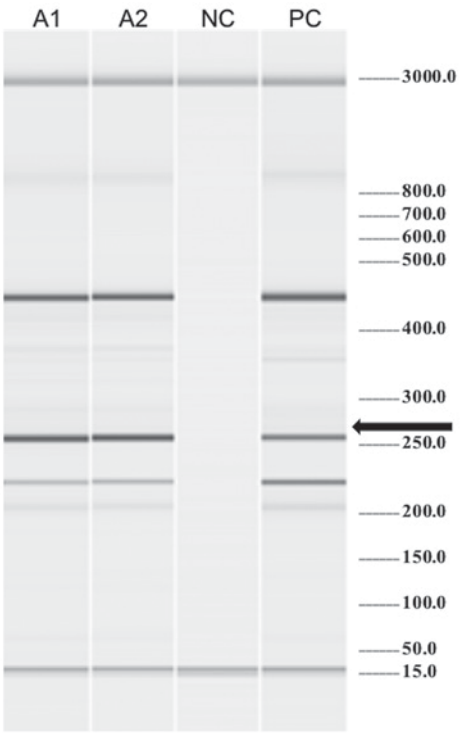

Figure 3. Case study 1: Molecular biology test revealed positivity for the JAK2V617F mutation (black arrow) in peripheral blood (A1 and A2, patient; CN, negative control; CP, positive control).

The Janus kinase 2 gene (*JAK2*; cytogenetic location: 9p24.1) provides instructions for making a protein that promotes the growth and division (proliferation) of cells. This protein is part of a signaling pathway called the JAK/STAT pathway, which transmits chemical signals from outside the cell to the cell's nucleus. The JAK2 protein is especially important for controlling the production of blood cells from hematopoietic stem cells. These stem cells are located within the bone marrow and have the potential to develop into red blood cells, white blood cells, and platelets.

The Philadelphia chromosome (chromosome 22) results from the reciprocal translocation of genetic material between chromosome 9 and chromosome 22, and contains the fusion gene *BCR-ABL*, which codes for a tyrosine kinase signaling protein that causes the cells to divide uncontrollably (particularly CML cells).

From 2007 to 2015, at least 42 patients with this double mutated phenotype were reported in the literature (10,12,15,16). Moreover, the italian group of Pieri *et al* (17) studied 314 patients with CML and identified 8 cases (2.55%) with concomitant *JAK2*V617F mutation. Pagnano *et al* detected only one case with *JAK2*V617F mutation among 55 cases of CML analyzed (13).

Among these different studies reported, several patterns were described: i) Initially diagnosed with CML and treated

Table II. Results over time and therapy prescribed for case study 2.

	Time point					
	2005	2009	2013	2016	2017	
Characteristic	March	March	September	February	January	August
Platelets (x10^9/l)	1022	478	684	909	413	252
Hemoglobin (g/dl)	14.6	14.7	12.2	13.1	14.1	11.8
Leucocytes (x10^9/l)	9.4	6.9	22.4	30.1	38.4	7.3
JAK2V617F mutation	-	-	-	-	Positive	-
BCR/ABL t(9;22) (FISH)	-	-	-	-	Positive 17% (atypical pattern)	-

The patient was started on HU for thrombocytosis, with subsequent increase in dose and the addition of TKI. A few months later, TKI was suspended and HU treatment was maintained. *BCR/ABL*, BCR RhoGEF and GTPase activating protein-ABL proto-oncogene 1 non-receptor tyrosine kinase; FISH, fluorescent *in situ* hybridization; HU, hydroxyurea; TKI, tyrosine kinase inhibitor.

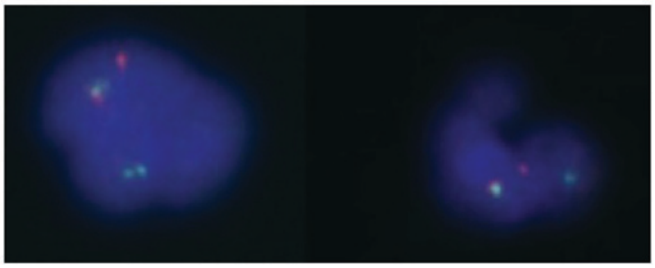

Figure 4. Case study 2: FISH test. It revealed positivity for the the BCR-ABL translocation with an atypical pattern, in which a unique fusion signal is detected. BCR/ABL, BCR RhoGEF and GTPase activating protein-ABL proto-oncogene 1 non-receptor tyrosine kinase; FISH, fluorescent *in situ* hybridization

with imatinib that proceeded to a *JAK2*V617F myeloproliferative phenotype; ii) initially diagnosed with CML coexisting with *JAK2*V617F mutation positive PV, ET or PMF; or iii) initially diagnosed with *JAK2*V617F mutation positive PN-MPN, ET more rarely, evolving years later to CML (10). Commonly, men above 50 years old were the most frequently affected (10).

A question still has to be clarified: Which is the first anomaly to occur? Several working groups reported that in some cases of PN-MPNs that evolved to CML, *JAK2*V617F mutation was the first leukemogenic event and BCR-ABL the second positive clone (10). Moreover, it was also speculated that *JAK2*V617F mutations are present in hematopoietic stem cells, with an additional *BCR-ABL* translocation being subsequently acquired in a sub-clone (10,18). However, other groups didn't confirm these results, and postulate that the two anomalies are present since the beginning of the process (10). Indeed, about the amount of cellular clones involved, there are reports that state that two different clones are involved, with the phenotypic expression depending on which one of the aberrations is 'dominating', as a result of therapy targeted to the other anomaly (10,11,19,20). On the other hand, there are some authors evidencing that all the myeloid cells bear *JAK2*V617F mutation, including granulocytic and erythroid colonies, while *BCR-ABL* translocation is confined to a small compartment of myeloid progenitor cells, only in granulocytic colonies (10). In contrast, other reports showed the simultaneous presence of both *BCR-ABL* transcript and *JAK2*V617F mutation in the majority of granulocytic and erythroid colonies at the time CML diagnosis was established, corroborating the hypothesis that only one cellular clone is bearing concomitantly the two anomalies (10,11).

Therefore, the phenotypic heterogeneity can be the result of the expression of a pre-existing mutated clone previously 'silent' or of the accumulation of several genetic events conferring genetic instability and leading to a 'new' anomaly (12).

As far as we know from literature revision, there are no other reports of positivity for *JAK2* mutations, other than V617F, with the concomitant presence of *BCR-ABL* translocation.

One of the diagnostic criteria for ET, is the absence of the Ph chromosome. *BCR-ABL* positive ET without features of CML in blood and bone marrow is a rare entity and constitute less than 5% of ET diagnosis. Some authors have proposed to consider those cases as CML associated with a rather poor prognosis because of the high tendency to progress to myelofibrosis and blastic transformation after a few to several years (16,20,21).

An important difference between *BCR-ABL* positive ET and *BCR-ABL* positive CML at time of presentation is the absence of splenomegaly in the first situation (16).

The bone marrow in *BCR-ABL* positive ET is featured by predominant smaller than normal and hypo/mononucleated megakaryocytes caused by BCR-ABL gene and protein induced maturation defect of the hematopoietic stem cells. This contrasts with clustered enlarged megakaryocytes in *BCR-ABL* negative ET due to growth advantage and proliferation of constitutively activated *JAK2* or *MPL* somatic mutated megakaryocytes (16).

The first patient reported had diagnostic features that matched CML and ET. However, his overall clinical presentation including bone marrow features was more commonly suggestive of ET. Since the t(9;22) was positive in FISH, according to the results, there should have been found a positive result in molecular biology tests as well. Moreover, no Ph

chromosome was detected by karyotype. The second patient reported was more suggestive of ET and did not have typical clinical, nor morphologic findings for CML. The t(9;22) was also positive only by FISH, with a negative result in molecular biology tests. In this case it was not possible to evaluate karyotype due to metaphases absence.

In both patients, search for *JAK2*V617F mutation and *BCR-ABL* was concomitant, making very difficult to know if both mutations were present from the beginning or the order of appearance of each one of them. The fact that the study has been performed before therapy institution, excludes the possible inhibitory effect of it over one of the altered clones, making the other more expressive.

Given the above, several questions have to be raised: Are these genomic alterations found in these two patients and their atypical pattern really true and clinically significant or are they false positive results? May those be new/distinct clinical entities? Should we consider Ph positive ET as distinct entity, separate from Ph negative ET and Ph positive CML?

As mentioned above, studies describing cases initially diagnosed with *JAK2*V617F mutation positive PN-MPN, evolving later to CML, were rarely ET patients (10), in contrast to our report.

Although, the concomitant presence of these two anomalies in these patients didn't seemed to exclude the diagnosis of ET, at diagnosis or in some point of their clinical course, both patients evidenced a distinct clinical (thrombocytosis with associated leukocytosis) or morpho-histological (megakaryocytic) phenotype from what was expected for ET with isolated *JAK2*V617F positive or Ph positive CML, but apparently not influencing the course of the disease.

Both patients showed an atypical pattern for *BCR-ABL* translocation search by FISH, said to be atypical because only one fusion signal was observed, instead of the two signals expected, with a percentage of *BCR-ABL* translocation of approximately 20%. RT-PCR was performed using only a single primer pair, failing the identification of p190 and p210 transcripts of *BCR-ABL* fusion gene, and making the presence of BCR-ABL tyrosine kinase activity questionable. Real time PCR was a distinct possible technique to be used for the identification and quantification of *BCR-ABL* p210 (mainly b3a2 and b2a2 types) transcripts, however it was not performed.

Since no *BCR-ABL* transcripts were detected by RT-PCR, one hypothesis is that the unique fusion signal detected by FISH could correspond only to der(9), and not to Ph chromosome with associated tyrosine kinase activity (on chromosome 22). Confirmation could be achieved doing FISH in metaphases, which was only possible in the first case, since the second patient had no metaphases to allow it. This way, we were not able to be sure of the localization of break points and consequent fusion.

On the other hand, a missense on the primer site or the probe pairing region could also explain such RT-PCR result, but there is a vast experience with the used primers, internationally designed and certified.

Regarding clarification of the possible mechanism of association of *JAK2*V617F mutation and a 'true' *BCR-ABL* translocation involved in our patients, it would be useful to analyze *JAK2*V617F mutation and *BCR-ABL* gene in each colony of BFU-E or CFU-C.

Given the above, probably these cases correspond to two patients with a variant ET, in which we possibly can hypothesize that the presence of der(9) chromosome might be involved in those phenotypic differences. As far as we are aware, no other studies describing these two 'truly' genomic alterations have found a *BCR-ABL* aberrant pattern similar to our cases. However, Larsen *et al* (22). Described the case of four patients *JAK2*V617F positive with associated distinct karyotypic aberrations [including der(9;18)], presenting with a distinct clinical and prognostic profile. Likewise, another study also reported the association of der(9) chromosome and acute lymphoblastic leukemia (23), with prognostic impact.

Moreover, WHO does not currently address the classification of MPNs that have more than one genetic abnormality, but it is well established that the presence of additional co-operating mutations in myeloid genes (along with other important risk factors) has a straight relationship with phenotype and clinical outcome definition (24,25). Cytogenetic analysis allows to identify subgroups of patients with a distinct phenotype and prognostic profile, and should be performed in conjunction with *JAK2* mutation analysis PN-MPNs patients (22).

Furthermore, the concomitant presence of two molecular markers is well defined for certain diseases, and raises several issues, including the best therapeutic strategy to adopt. But, therapeutic decisions should not be based only on molecular biology test results (18).

CML can express on the background of a *JAK2*V617F positive PN-MPN, and treatment with TKI might reveal/make more expressive the PN-phenotype. It is of great importance to recognize and investigate the association of both anomalies, especially in CML patients who have an unusual clinical/laboratorial course, with hemoglobin and/or platelets count increase, or when they do not respond to therapy, making the diagnosis of other MPNs to have practical therapeutic consequences.

It seems that for these complex patients the most efficient therapeutic choice is to associate a TKI with a *JAK2* inhibitor (10,11).

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

FM and APA contributed to the conception and design of the work, acquisition, analysis and interpretation of data; drafted and wrote the manuscript, revising it critically for important intellectual content; were accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work were appropriately investigated

and resolved. TM, PSS, RC, SM, SS, JFV and FL analyzed the data and revised the paper. SR provided the histological images and revised the paper. All authors approved the final manuscript.

Ethics approval and consent to participate

Patient anonymity and consent was guaranteed, in agreement with the Declaration of Helsinki. the Institutional Ethic Board of Hospital of São Francisco Xavier, West Lisbon Hospital Centre (ref. no. 120/CE_2009) approved this study.

Consent for publication

Patient anonymity and consent was guaranteed, in agreement with the Declaration of Helsinki.

Competing interests

The authors declare that they have no competing interests.

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