

immunologic, probably IgE-mediated, and there is a latent period between onset of exposure and the appearance of symptoms.<sup>1</sup> With regard to diagnosis, specific bronchial challenge in the laboratory is considered the gold standard. When this is not available, specific bronchial challenge in the workplace is very useful.<sup>2-4</sup> These patients progress well if exposure is avoided.<sup>2,5</sup> However, 70% of them may continue to present symptoms and require treatment, even in the absence of exposure.

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## Pulmonary Embolism as a First Manifestation of Intracardiac Extension of an Endometrial Stromal Sarcoma<sup>☆</sup>



### Embolismo pulmonar como primera manifestación de extensión intracardiaca de un sarcoma del estroma endometrial

To the Editor:

We report the case of a 47-year-old patient with iodinated contrast allergy and hypertension, diagnosed 2 years previously with low-grade malignant endometrial stromal sarcoma (ESS) treated with hysterectomy, double adnexectomy and bilateral pelvic lymphadenectomy. One year later she presented left retrosupravescular tumor recurrence that could only be partially resected, and received neoadjuvant radiation therapy and hormone therapy in the form of tamoxifen.

The patient presented with a one-week history of dyspnea on minimal effort. No significant findings were seen on chest X-ray. Significantly, a rapid ELISA test showed D-dimer of 1.141 ng/ml, so lung scintigraphy was performed that confirmed bilateral pulmonary thromboembolism. Furthermore, a large mass in the right atrium that prolapsed into the ventricle during diastole with extension into the inferior vena cava (IVC) was observed on transthoracic echocardiogram (Fig. 1A). Magnetic resonance imaging (MRI) of

the chest and abdomen (Fig. 1B) confirmed thrombosis occupying almost the entire lumen of the common iliac veins and the IVC, extending up to the right atrium. Gadolinium uptake was observed on inferior vena cava imaging, supporting the diagnosis of tumor thrombosis.

Surgical intervention was ruled out in view of the partial resection of the pelvic tumor performed one year previously at the time of disease recurrence and because of her concomitant pulmonary thromboembolism. Enoxaparin 60 mg every 12 h and chronic oral anticoagulation were administered. Subsequent clinical progress was favorable, and after 30 months of follow-up the patient remains asymptomatic with an excellent performance status. Resolution of the thrombus in the right atrium and almost complete recovery of IVC patency have been observed on follow-up ultrasound and MRI.

ESS is a rare malignancy that accounts for only 0.2% of cancerous uterine tumors. The 5-year survival rate is 80%-100%. However, 30%-50% of patients present disease recurrence, generally after a long period of latency.<sup>1</sup> Metastases most commonly occur in the vagina, the pelvis and in the peritoneal cavity. IVC tumor thrombosis and intracardiac tumor metastasis are extremely rare.<sup>2,3</sup> Thus, although the prognosis of these tumors is good, they can appear to behave in a more aggressive manner.

Inferior vena cava tumor thrombosis is relatively common in renal carcinoma, and in these cases MRI is usually performed to

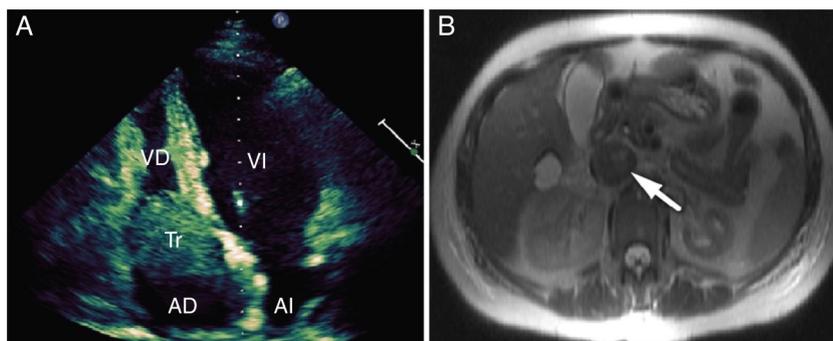


Fig. 1. (A) Transthoracic four-chamber ultrasound, apical view, showing large thrombus in the right atrium shifting toward the right ventricle during diastole. AD, right atrium; AI, left atrium; Tr, thrombus; VD, right ventricle; VI, left ventricle. (B) Abdominal magnetic resonance image of inferior vena cava thrombosis.

<sup>☆</sup> Please cite this article as: Garcipérez de Vargas FJ, Marcos G, Moyano Calvente SL. Embolismo pulmonar como primera manifestación de extensión intracardiaca de un sarcoma del estroma endometrial. 2014;50:498-499.

confirm anatomical continuity between the tumor and the renal vein and the vena cava. Treatment of choice is surgery, and outcome in the absence of intervention is poor. In the case reported here, it was difficult to confirm anatomical continuity since the patient had undergone hysterectomy and double adnexectomy 2 years previously. The prognosis of endometrial stromal sarcoma is good, and its evolution and behavior cannot be compared to the considerably more aggressive renal cancer.

In the case of IVC and intracardiac thrombi, surgery is recommended for excision of the tumor thrombosis, with or without IVC resection, in order to prevent sudden death due to pulmonary embolism or the development of congestive heart failure or death due to acute valvular obstruction.<sup>4</sup> We did not find any published cases of patients treated with anticoagulation only.

To conclude, it is safe to say that although surgery is the treatment of choice for IVC and/or intracardiac tumor thrombosis, for patients with advanced or inoperable disease or those who refuse surgery, chronic anticoagulation may also be a valid treatment option. In our view, there are probably many cases in which tumor thrombosis coexists with non-tumor thrombosis: it is easy to imagine that a lumen occupied by a tumor will favor the development of non-tumor thrombosis. This would explain the almost complete resolution of our case with anticoagulant treatment.

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## S1455X CFTR Mutation and Upper Airway Colonization With *Pseudomonas aeruginosa*<sup>☆</sup>



### Mutación S1455X del CFTR y colonización de vías aéreas altas por *Pseudomonas aeruginosa*

To the Editor:

Cystic fibrosis (CF) is a classic example of an autosomal recessive genetic disorder, and multiple variant forms of this disease have been identified. It is caused by CF transmembrane conductance regulator (CFTR) dysfunction resulting from CFTR gene mutations. Not all CFTR mutations are associated with disease expression. The S1455X mutation is very uncommon (0.22% prevalence in our patient population). Individuals with this mutation have only very mild symptoms, if any. We present the first report of twin brothers, both S1455X mutation-carriers, with *Pseudomonas aeruginosa* colonization of the upper airways.<sup>1–4</sup>

Patients A and B are 2-year-old monozygotic twin brothers. After birth, patient A was admitted to the neonatal intensive care unit for 7 days due to mild breathing difficulties. Routine neonatal immunoreactive trypsinogen screening results were close to the upper limit of normal (65 mcg/l; normal value <77 mcg/l). When patient A was 7 months old he suffered bronchitis, for which he received inhaled albuterol and fluticasone. At the age of 13 months, he was admitted to a pediatric intensive care unit with lethargy due to severe hyponatremic dehydration and hypochloremic and hypokalemic metabolic alkalosis. At that time a definitive diagnosis of CF was given (chloride sweat levels of 101.6 mEq/l and 105.8 mEq/l; mutations: F508del and S1455X). The patient has pancreatic sufficiency and normal growth (weight: 75th–90th percentile; height: 90th percentile). Serial pharyngeal swab cultures grew *Pseudomonas aeruginosa*.

Following his brother's diagnosis, at the age of 13 months patient B was also diagnosed with CF (chloride sweat levels:

80.7 mEq/l and 81.7 mEq/l, mutations: F508del and S1455X). Similarly, he has pancreatic sufficiency and good growth (weight, 50th percentile; height: 75th percentile). Repeated pharyngeal swab cultures grew *Pseudomonas aeruginosa*.

The case of these two brothers suggests that the S1455X mutation of the CFTR gene in combination with the F508del mutation may be associated with early *Pseudomonas aeruginosa* colonization of the upper airways. This observation has not been previously reported in the literature. In other reported cases of S1455X CFTR mutation, the sweat test was abnormal, but no respiratory disorders were detected.<sup>1,2</sup> Only one case of a child with mild pulmonary disease due to *Haemophilus influenzae* infection and persistent hyponatremia during a heat wave has been described.<sup>3</sup>

S1455X is a nonsense mutation causing premature transcriptional termination of CFTR. More specifically, the codon for serine at residue 1455 is replaced by a stop codon, hence the designation S1455X.<sup>1</sup> In the initial description from Mickle et al.,<sup>1</sup> the S1455X mutation was associated with isolated elevated chloride levels in sweat. *In vitro* testing predicted preserved CFTR function in lung and pancreatic cells.<sup>1</sup> Subsequently, Moyer et al.<sup>4</sup> suggested that the CFTR-S1455 chloride channel defect was caused by mispolarization to the lateral membrane instead of to the apical membrane.

The two cases previously described in the literature as compound heterozygotes for the F508del and S1455X mutations presented a mild phenotype in the sense that S1455X was associated with minor symptoms and a favorable prognosis, even when accompanied by such a severe mutation as F508del.<sup>2,3</sup> Although our pediatric patients are carriers of this same genotype, they appear to have a more severe clinical presentation than that predicted by other authors, leading us to speculate on the possibility of a predominant F508del mutation. Our cases underline the concept of a variable correlation between the CF genotype and phenotype.

## Authorship

Efthimia Kalampouka and Argyri Petrocheilou participated equally in the authorship of this letter.

<sup>☆</sup> Please cite this article as: Kalampouka E, Petrocheilou A, Kaditis AG, Doudounakis SE. Mutación S1455X del CFTR y colonización de vías aéreas altas por *Pseudomonas aeruginosa*. *Arch Bronconeumol*. 2014;50:499–500.