reveal some of the consequences of short-term consumption, but the pathophysiological mechanism by which the lung injury occurs, the substances responsible for it, and its correct treatment are still unknown.

A patient registry, as proposed by SEPAR, is now urgently needed to enable us to carry out a thorough analysis of the cases and shed light on this new entity. We must establish more precise diagnostic criteria, identify the substances responsible for lung damage, and produce solid scientific evidence to guide the proper management of these patients and to convey a clear message to the general population and health authorities about these devices.

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Symptomatic azygous vein thrombosis: Clinical case and literature review☆

Trombosis sintomática de la vena ácigos: caso clínico y revisión de la literatura

To the Editor:

Azygos vein thrombosis (AVT) and hemiazygos vein thrombosis (HVT) are rare entities. The etiopathogenesis is unknown, but these thromboses have been associated with predisposing factors, such as underlying azygos vein aneurysm (AVA)[1] or other prothrombotic factors. AVT in a normal azygos and hemiazygos vein is exceptional.[2] The azygos system provides the superior (SVC) and inferior vena cava (IVC) with an alternative access to the right atrium, so AVT is usually asymptomatic, making it difficult to diagnose and treat early. It can be complicated by pulmonary embolism (PE), vena cava syndrome (VCS) and even stroke in the case of cardiac shunt, which confers a worse prognosis.[3] This paper reports an acute, symptomatic case of AVT and HVT and reviews the most relevant aspects of this rare entity.

A 60-year-old woman, former smoker, receiving chemotherapy for a diagnosis of ovarian adenocarcinoma, presented with sudden dyspnea, heaviness in the upper limbs, and syncope. Physical examination revealed blood pressure 110/60 mmHg, heart rate 110 bpm, oxygen saturation 95%, erythema and facial edema, and no signs of collateral circulation or lymphadenopathies. On laboratory tests, hemoglobin was only 8.6 g/dl. Chest CT-angiogram showed extensive thromboses in the azygos and hemiazygos veins, with no signs of PE or VCS (Fig. 1). No findings of interest were observed on lower limb ultrasound or echocardiogram. Thrombophilia tests, including antiphospholipid antibodies, were negative. The patient was given weight-adjusted tinzaparin treatment and anticoagulation continued until the end of chemotherapy (9 months), with complete resolution of her respiratory symptoms and no evidence of complications. Repermeabilization of the AVT was observed in the follow-up CT.

We performed a Pubmed search for original and review articles using the term *"azygos vein thrombosis"*. Original articles were eligible for inclusion if AVT and/or HVT were identified. Abstracts, animal studies, and articles written in languages other than English or Spanish were excluded. The references for each article included in this review were also analyzed to identify other studies of interest. We found a total of 216 eligible studies, published up to June 2020. Nineteen studies met the inclusion criteria and all reported

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Table 1
Predisposing factors, clinical presentation and treatment in studies on azygos vein thrombosis.

Reference	Year of publication	Sex	Age	Predisposing factor	Clinical presentation	Adverse event(s)	AVT treatment	Death
Savu et al.[1]	2020	Female	74	AVA	Chest pain, cough, and dyspnea	AVT	Surgical resection	No
Galeano-Valle et al.[16]	2019	Male	75	VCS due to tuberculous pleural effusion undergoing radiation therapy at the age of 24	Edema of upper limbs	AVT in SVC, brachiocephalic, iliac and IVC and distal part of the azygos vein. VCS	Rivaroxaban	No
Abdulla et al.[18]	2018	Male	60	Cholangiocarcinoma	Asymptomatic	AVT	Not specified	Not specified
Liew et al.[3]	2017	Male	57	ERCP due to choledocholithiasis	Acute chest pain and dyspnea	AVT	None	No
Lee et al.[12]	2016	Female	73	Urinary tract infection, fracture of the femur	Fever	Transient antiphospholipid syndrome and AVT	Antibiotics	No
Sherif et al.[14]	2015	Male	26	PICC implanted for antibiotic treatment of complicated discitis	Fever, pleuritic chest pain, and cough	AVT	Heparin followed by warfarin	No
Gheith et al.[15]	2014	Male	18	Renal transplantation, central venous catheter, chylothorax	Dyspnea and hypoxemia	DVT in left and right internal jugular vein, bilateral subclavian veins, brachiocephalic vein, incomplete thrombosis of SVC, and AVT	Warfarin, pleural drainage, octreotide	No
Pradhan et al.[13]	2013	Female	32	IDA (heroin) Epidural abscess	Chest pain	AVT and septic PE	Antibiotics	No
Kurihara et al.[4]	2012	Female	73	AVA	Asymptomatic	AVT	Surgical resection	No
Kang et al.[2]	2012	Male	51	No	Dyspnea, chest pain, and fever	Septic AVT with septic PE	Antibiotics	No
Smith et al.[17]	2011	Male	33	Congenital inferior vena cava abnormality with azygos continuation	Nephritic colic and hematuria	AVT	Indefinite anticoagulation	No
Yang et al.[5]	2011	Female	75	AVA	Asthenia and chronic cough	ATV and PE	Heparin (4 days) followed by warfarin for 2 months	No
Ishikura et al.[6]	2010	Female	51	AVA	Asymptomatic	AVT	Surgical resection	No
Probst et al.[19]	2010	Female	81	Renal carcinoma	Not specified	AVT, thrombosis of the IVC and the left renal vein	Not specified	Not specified
Gnanamuthu et al.[7]	2008	Male	73	AVA	Cough and mild dysphagia	AVT	Surgical resection	No
Irurzun et al.[8]	2008	Male	77	Endovascular treatment of AVA	Cough, wheezing, and hiccups	AVT	None	No
Nakamura et al.[9]	2007	Female	37	AVA	Palpitations and chest pain	ATV and PE	Ineffective anticoagulation and urgent surgical resection	No
Gomez et al.[10]	2004	Male	20	AVA	Chest pain	AVT	Surgical resection	No
Icard et al.[11]	1999	Male	68	AVA	Chest pain	AVT	Surgical resection	No

AVA: azygos vein aneurysm; AVT: azygos vein thrombosis; DVT: deep vein thrombosis; ERCP: endoscopic retrograde cholangiopancreatography; IDA: inhaled drug abuser; IVC: inferior vena cava; PICC: peripherally inserted central catheter; PE: pulmonary embolism; SVC: superior vena cava; VCS: vena cava syndrome.

isolated clinical cases (Table 1). Of the 19 patients included, male sex was slightly more predominant (57.8%) and the mean age was 55 years. AVA was the most frequent predisposing factor in 47.3% of cases,[1,4–11] followed by septic thrombosis (15.78%)[2,12,13] and intravenous catheters (10.5%).[14,15] Other etiologies included other prothrombotic factors[3,16] and congenital malformations.[17] Although the high prevalence of venous thromboembolism (VTE) in cancer patients is well known, AVT associated with cancer is unusual.[18,19]

Isolated AVT was conventionally considered as asymptomatic deep vein thrombosis (DVT) in an unusual site, until it was associated with complications such as PE or VCS. In our patient, the syncopal episode, together with the clinical picture suggestive of VCS, confirmed the presence of AVT and HVT in the imaging tests. In most cases included in the review, AVT was symptomatic (84.2%), with chest pain being the most frequent symptom (42.1%), followed by cough (26%) and dyspnea (21%). The most frequent complications included thrombosis in other sites (15.7%),[15,16,19] followed

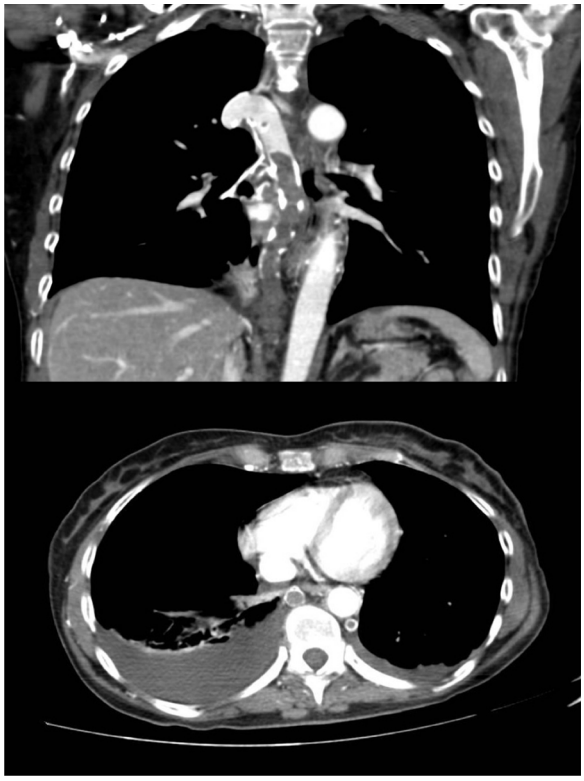

Figure 1. Extensive azygos and hemiazygos vein repletion defects, with no signs of thrombosis in main, lobar, or segmental pulmonary arteries.

by PE (10.5%),[5,9] septic PE (10.5%),[2,13] VCS (5.2%),[16] and transient antiphospholipid syndrome (5.2%).[12]

Chest CT-angiogram is the test of choice for the diagnosis of AVT, while a CT-venography should be considered if VCS is suspected. In thrombosed AVAs, the use of dynamic multidetector CT with ECG to assess myocardial damage has been proposed.[5]

As AVT is considered thrombosis in an unusual site, the treatment recommendations have been extrapolated from published studies on VTE.[20] Almost one third (31.6%) of AVT cases were treated with anticoagulants, while in 1 case, anticoagulation was ineffective and surgical resection was required.[9] Antibiotics are the first line of treatment in AVT associated with infection and/or septic PE,[2,12,13] although anticoagulation in these cases may be controversial. Some cases of endovascular treatment, thrombectomy, and removal of infected devices have been reported.[11,12]

Despite the association of AVA with AVT and PE, treatment of asymptomatic aneurysm is not well established, and experts recommend radiological follow-up.[4] Furthermore, there is no established consensus for asymptomatic thrombosed AVA, and treatment can range from indefinite anticoagulation to surgical resection to prevent PE. In our series, 36.8% of the symptomatic and/or thrombosed AVAs underwent surgical resection without subsequent anticoagulation.[1,4,6,7,9–11] In VCS secondary to AVT, the first-line treatment is anticoagulation. It is effective in up to 88% of patients and can be combined with percutaneous stent placement for immediate symptomatic relief and chemotherapy and/or radiotherapy with long-term curative or palliative intent. According to experts, anticoagulation for the treatment of VCS due to thrombosis should be maintained indefinitely.[21] In the series reviewed, there were no deaths in follow-up.

In conclusion, the importance of this clinical case lies in the rare presentation of a DVT in an unusual site in an anatomically normal azygos system. This is an extremely rare presentation in isolation that we were able to diagnose and treat promptly due to the clinical presentation suggestive of VCS.

Conflict of interests

Luis Jara Palomares has received honoraria for speaking engagements and for travel and accommodation from Rovi, Pfizer, Menarini, Leo-Pharma and GSK, unrelated to this manuscript. Maria Isabel Asensio Cruz has received honoraria for travel and accommodation from Rovi, Novartis and Teva, unrelated to this manuscript. Raquel Morillo Guerrero has received honoraria for speaking engagements and for travel and accommodation from Pfizer, Menarini and GSK, unrelated to this manuscript. The other authors state that they have no conflict of interests.

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Tuberculosis contacts study: Organization and prevalence of latent tuberculosis infection☆

Estudio de contactos de pacientes con tuberculosis: organización y prevalencia de la infección tuberculosa latente

To the Editor:

Contacts tracing of patients with tuberculosis (TB) is a priority for the control of the disease in countries with low prevalence and high economic resources,[1,2] as stated in the Plan for the Prevention and Control of Tuberculosis in Spain, which underlines the need to intensify contact tracing and coordination among all the health centers and teams involved.[3] However, few studies in Spain have analyzed the organization of contacts tracing programs: most have been performed in specific geographical areas and focus on evaluating such programs to identify their weaknesses and work towards improving them.[4,5]

This prospective, observational cohort study of the contacts of tuberculosis patients was therefore aimed at describing the organization of these programs in Spain and the prevalence of latent tuberculous infection among the contacts studied.

Contacts of patients diagnosed with TB between January 2018 and December 2019 were identified and included in the national registry of SEPAR's Integrated Tuberculosis Research Program (PII-TB), which is accessed by user names and passwords provided to the members of the PII-TB Task Force The study was approved by the Research Ethics Committee of all participating centers. Twelve centers from 6 Spanish autonomous communities participated in the study.

The following definitions were established:

a) *Initial index case*: a person of any age diagnosed with TB in a specific household or other comparable environment in which others may have been exposed.
b) *Contact*: any person who has been exposed to an index case and classified according to the time of exposure as: 1) habitual: contact was repeated and occurred more than once a week; and 2) sporadic: only one contact occurred or, if repeated, occurred less than once a week. In any case, to be sporadic, the period of contact had to be less than 6 h.
c) *Secondary case*: a person diagnosed with TB who was identified from among the individuals studied as contacts.
d) *Latent tuberculosis infection (LTBI):* tuberculin skin test (TST) with induration diameter of 5 mm or more and/or positive interferon-γ release assay (IGRA), with no evidence of active disease. The QuantiFERON-TB GOLD in-Tube IGRA was used with a cut-off point of 0.35 IU/ml. The responsible investigator determined which TST and IGRA were to be used and the order in which they were performed.
e) *Dual strategy*: use of both diagnostic techniques, TST and IGRA, regardless of the sequence.

Proportions were compared between groups using the Chi-square test and the 2-tailed Fisher test when the expected values were less than 5. Quantitative variables were compared using the Student's t-test or its non-parametric equivalent, the Mann–Whitney U test. The prevalence of LTBI among contacts was calculated taking into account the total number of contacts. A p-value of less than 0.05 was considered significant.

We analyzed 1035 contacts from 265 index cases, 525 women and 510 men, with a mean age of 37.96 ± 20.13 years; 777 (75.1%) were Spanish natives and 413 (39.9%) were household contacts. Contacts tracing was conducted in specialist tuberculosis clinics in 769 cases (74,2%). Table 1 shows the differences between different healthcare sites where the tracing study was performed.

TST was performed in 844 contacts (81.5%) and IGRA in 469 (45.3%), while both tests were performed in 348 (33.6%). Of the 444 in whom the TST was negative, a second determination was made in 90.7% with a conversion rate of 2.7%; these percentages were 58.8% and 5.2% (9/289), respectively, for the IGRAs. LTBI was diagnosed in 346 (33.4%) and depending on the diagnostic strategy, the prevalence was 48.2% if both TST and IGRA were performed, 27.4% if TST was used alone, and 40.4% if IGRA was used alone (p = 0.01). In 126 contacts, the index case had negative sputum smear and culture or extrapulmonary disease. Of these, 97 (76.9%) were seen in specialist tuberculosis clinics, and LTBI was detected in 24.6% (31/126).

TB was diagnosed in 17 contacts (1.6%): in all of these, the index case had a positive culture.

In our series, LTBI is slightly less prevalent than the 40% to 57% reported in previous studies published in Spain.[4,6] We believe that this may be partly due to the uneven use of diagnostic techniques, since LTBI rates were significantly higher in cases in which a dual strategy was used. Although there is no clear advantage of TST over IGRA, or vice versa, performing both tests together to establish the diagnosis of LTBI improves diagnostic sensitivity.[7] In addition the conversion rate of the IGRA is also higher than that of TST.[8,9] We found that TST and IGRA were performed simultaneously in only 33% of patients, and if the initial test was negative, a second determination was made in a higher percentage of patients undergoing TST than IGRA. We therefore believe that the dual strategy is the most appropriate, and if the initial tests are negative, they should be repeated 8–12 weeks later to determine whether there are conversions; this is one of the aspects to be improved in the performance of contact tracing studies.

Another interesting finding of our study is that tracing of more than 2/3 of the contacts was conducted by a specialist tuberculosis clinic. These facilities differ clearly from other healthcare sites: they perform a higher percentage of dual diagnostic techniques, track contacts outside the family setting, and follow up index

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