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Molecular characterization of *Staphylococcus aureus* causing menstrual toxic shock syndrome in a young woman

Caracterización molecular de Staphylococccus aureus, *agente causal del síndrome del shock tóxico menstrual en una mujer joven*

Toxic shock syndrome (TSS) is a rare life-threatening disease first described by Todd and Fishaut in 1978. The most characteristic symptoms are fever, rash, hypotension, desquamation and the involvement of multiple organ systems.[1] Menstrual TSS (mTSS) is defined when it appears from the beginning of the menstruation and up to four days after.[2] mTSS incidence has been reported to be 0.69 in 100,000 menstruating women per year and has been associated with high morbidity and mortality rate in previously healthy women.[3]

mTSS is caused by superantigen-producing *Staphylococcus aureus* (SA) or group A *Streptococcus,* and has been associated with the use of different vaginal devices as tampons or menstrual cups.[4] SA superantigen, named toxic shock syndrome toxin-1 (TSST-1), is encoded by *tst* gene and is responsible for mTSS by its ability to trigger excessive and non-conventional T-cell activation with consequent downstream activation of other cell types, and cytokine/chemokine release.[5]

We report a case of a 15-year-old menstruating woman who was hospitalized in the Intensive Care Unit (ICU) with suspicion of septic shock in the context of purulent vaginal discharge. The presented symptoms were malaise, fever (38.9 °C), sore throat, diarrhoea, rash and painful genital ulcers of 3 days of evolution. Physical examination was remarkable for a low blood pressure (80/50 mmHg), diffuse erythematous macular rash and conjunctival hyperaemia. Laboratory assessments on admission revealed elevated inflammatory markers (value obtained – reference range) (CRP 218 mg/L – 0.2–5 mg/L; PCT 26.65 ng/mL – <0.05 ng/mL), acute renal injury (creatinine 3 mg/dL – 0.51–0.95 mg/dL), anaemia (haemoglobin 10.5 g/dL), thrombocytopenia (101×10^9 platelets/L) and associated coagulopathy (D-dimers 6634 ng/mL – 0–243 ng/mL). Upon ICU admission, several samples were sent to the laboratory for bacteriological study and SA was isolated from vaginal, nasal, rectal and axillary swabs, pointing out the mTSS as the most probable diagnosis. Blood cultures remained negative. Antibiotic susceptibility testing was performed with Panel Type 33 of MicroScan WalkAway using the breakpoints recommended by The European Committee on Antimicrobial Susceptibility Testing (http://www.eucast.org).

The four SA strains showed the same resistance phenotype (penicillin, erythromycin and clindamycin inducible (MLSBi)); they were sent to the University of La Rioja for detection of (1) virulence genes: *tst* (encoding TSST-1 toxin), *pvl* (encoding Panton-Valentine-Leucocidin) and *sea*, *seb* and *sec* (encoding enterotoxins A, B and C); (2) antimicrobial resistance genes (*blaZ* and *ermA/ermB/ermC/ermT*); (3) molecular typing (*spa*-typing and multi-locus-sequence-typing); (4) immune evasion cluster (IEC) system, present in most human SA isolates (the IEC system includes seven different types: from A to E).[6]

The four isolates were typed as MSSA-CC30-t012 and IEC-type A, they carried the *tst* gene (verified by PCR/sequencing) but not *pvl* and they carried the *blaZ* gene (Table 1); they also carried the *sea* gene but not *seb* or *sec* genes. The prevalence of CC30 SA has been considerably reported in several European countries[7,8]; and a study performed in the UK revealed a strong association of the *tst*-positive CC30 SA lineage with mTSS and TSS cases.[9]

However, mTSS primarily remains a clinical diagnosis, and indeed, the isolation of SA *tst*$^+$ is not required for diagnosis of the disease.[5] Moreover, in Spain and other countries in Europe, TSS is not a notifiable illness, so the clinical, microbiological, and toxigenic features of TSS remain poorly described.

The patient was empirically treated with cefotaxime and metronidazole. Metronidazole was discontinued and clindamycin was added when SA was reported. After antibiotic susceptibility testing, treatment changed from cefotaxime to cloxacillin and, since the patient was presenting a favourable evolution, clindamycin was maintained. The patient was discharged from ICU setting 2 days after admission, and sent home on the 8th day of hospitalization.

This case evidences the persistence of mTSS cases, which may be fatal, even leading to patient's death.[10] Thanks to the early diagno-

Table 1
Characterization of the four *Staphylococcus aureus* isolates recovered from the patient with menstrual toxic shock syndrome.

Sample	Molecular typing		Antimicrobial resistance		Virulence genes	IEC-type
	spa-type	CC	Phenotype[a]	Genotype		
Vaginal	t012	CC30	PEN, ERY, CLI[b]	*blaZ*, *erm*(A)	*tst*, ***sea***	A
Nasal	t012	CC30	PEN, ERY, CLI[a]	*blaZ*, *erm*(A)	*tst*, ***sea***	A
Rectal	t012	CC30	PEN, ERY, CLI[a]	*blaZ*, *erm*(A)	*tst*, ***sea***	A
Axillary	t012	CC30	PEN, ERY, CLI[a]	*blaZ*, *erm*(A)	*tst*, ***sea***	A

[a] PEN: penicillin; ERY: erythromycin; CLI: clindamycin.
[b] Inducible resistance.

sis and the prompt implementation of vital support and antibiotic treatment, our patient had a good outcome.

Conclusions

Due to its rarity and initially unspecific symptoms, patients with mTSS are at risk of misdiagnosis. Even though molecular methods are not available in many laboratories, its implementation should be considered since they represent a possibility for faster diagnostics, and to obtain more information for the clinical and epidemiological surveillance of mTSS/TSS-associated SA lineages.

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References

1. Todd J, Fishaut M, Kapral F, Welch T. Toxic-shock syndrome associated with phage-group-I staphylococci. Lancet. 1978;2:1116–8.
2. Centers for Disease Control and Prevention. Toxic shock syndrome (other than streptococcal) (TSS) 2011 case definition. Available from: http://www.cdc.gov/nndss/conditions/toxic-shock-syndrome-other-than-streptococcal/case-definition/2011/.
3. DeVries AS, Lesher L, Schlievert PM, Rogers T, Villaume LG, Danila R, et al. Staphylococcal toxic shock syndrome 2000–2006: epidemiology, clinical features, and molecular characteristics. PLOS ONE. 2011;6:e22997.
4. Schlievert PM, Davis CC. Device-associated menstrual toxic shock syndrome. Clin Microbiol Rev. 2020;33, e00032-19.
5. Pierson JD, Hansmann MA, Davis CC, Forney LJ. The effect of vaginal microbial communities on colonization by *Staphylococcus aureus* with the gene for toxic shock syndrome toxin 1 (TSST-1): a case–control study. Pathog Dis. 2018;76:fty015.
6. Mama OM, Morales L, Ruiz-Ripa L, Zarazaga M, Torres C. High prevalence of multidrug resistant *S. aureus*-CC398 and frequent detection of enterotoxin genes among non-CC398 *S. aureus* from pig-derived food in Spain. Int J Food Microbiol. 2020;320:108510.
7. Tavares A, Faria NA, de Lencastre H, Miragaia M. Population structure of methicillin-susceptible *Staphylococcus aureus* (MSSA) in Portugal over a 19-year period (1992–2011). Eur J Clin Microbiol Infect Dis. 2014;33:423–32.
8. Layer F, Ghebremedhin B, König W, König B. Heterogeneity of methicillin-susceptible *Staphylococcus aureus* strains at a German University Hospital implicates the circulating-strain pool as a potential source of emerging methicillin-resistant *S. aureus* clones. J Clin Microbiol. 2006;44:2179–85.
9. Sharma H, Smith D, Turner CE, Game L, Pichon B, Hope R, et al. Clinical and molecular epidemiology of staphylococcal toxic shock syndrome in the United Kingdom. Emerg Infect Dis. 2018;24:258–66.
10. Tang YW, Himmelfarb E, Wills M, Stratton CW. Characterization of three *Staphylococcus aureus* isolates from a 17-year-old female who died of tampon-related toxic shock syndrome. J Clin Microbiol. 2010;48:1974–7.

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Anisocoria and optic neuritis associated with *Mycoplasma pneumoniae* infection

Anisocoria y neuritis óptica en infección por Mycoplasma pneumoniae

Although the most common clinical form of infection by *Mycoplasma pneumoniae* (*M. pneumoniae*) is respiratory, this microorganism can cause extrapulmonary manifestations, the most serious of which is neurological[1]. We report here a case with anisocoria and optic neuritis.

This was a 32-year-old man with no previous medical history who had a two-week history of productive cough, dyspnoea, low-grade fever, nasal congestion and left hearing loss. Chest X-ray (Fig. 1, upper) revealed an infiltrate in the right upper lobe. *Legionella pneumophila* and pneumococcal urinary antigen tests were negative and treatment was started with amoxicillin/clavulanic acid 875/125 mg/8 h.

Two days later, the patient had not improved and attended Accident & Emergency; he had tachypnoea, with a baseline saturation of 88%, which rose to 95% with nasal cannula at 2 lpm, HR 46 bpm, blood pressure 124/68 and rhonchi in the upper right lung field.

Tests revealed leucocytosis with neutrophilia, coagulopathy (INR 1.3) and C-reactive protein of 103 mg/l, and a repeat chest X-ray showed no changes. Treatment was escalated to ceftriaxone 2 g/24 h with levofloxacin 500 mg/24 h and the patient was admitted to internal medicine.

On day three of admission he developed anisocoria, with greater mydriasis in his left eye. CT scan of the brain showed no acute intracranial findings. Pilocarpine eye drop test showed involvement of the left third cranial nerve.

CT angiogram of the head ruled out vascular injury and MRI ruled out cavernous sinus pathology, showing right maxillary sinusitis and left ethmoid sinus retention cyst (Fig. 1, lower). After 24 h, the anisocoria resolved spontaneously.

Multiplex PCR was carried out on nasopharyngeal exudate and sputum, which was positive for *M. pneumoniae* and negative for coronavirus, MERS-CoV, rhinovirus/enterovirus, influenza and parainfluenza virus, metapneumovirus, adenovirus and respiratory syncytial virus. Serum was also positive for *M. pneumoniae* IgM. HIV, syphilis and hepatotropic virus serologies were all negative. Azithromycin 500 mg/24 h for seven days was prescribed.

Four days later, the patient consulted once more due to loss of visual acuity in his left eye. Visual field testing revealed a diffuse loss of sensitivity with a superior altitudinal visual field defect in the left eye and visual acuity of 0.5. Lumbar puncture ruled out infection of the central nervous system. As parainfectious retrobulbar optic neuritis was suspected, he was started on corticosteroid therapy and made a full recovery.

At subsequent check-ups, the electroencephalogram, cervical spine magnetic resonance imaging and brain magnetic resonance angiography were normal, and the follow-up lumbar puncture showed no oligoclonal bands. Blood aquaporin 4 antibodies and myelin oligodendrocyte glycoprotein antibodies were negative, but he had a mild sustained IgG2 deficiency. After seven weeks, he continued to be IgM positive, with IgG seroconversion against *M. pneumoniae* (signal 1.41).