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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.

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.

This case evidences the persistence of mTSS cases, which may be fatal, even leading to patient's death.[10] Thanks to the early diagnosis 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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Anisocoria y neuritis óptica en infección por *Mycoplasma pneumoniae*

Anisocoria and optic neuritis associated with Mycoplasma pneumoniae *infection*

Aunque la forma clínica más frecuente de la infección por *Mycoplasma pneumoniae* (*M. pneumoniae*) es la afectación respiratoria, este microorganismo puede causar manifestaciones extrapulmonares, siendo las neurológicas las más graves[1]. Describimos un caso con anisocoria y neuritis óptica.

Se trata de un varón de 32 años sin antecedentes con cuadro de 2 semanas de tos productiva, disnea, febrícula, congestión nasal e hipoacusia izquierda. En la radiografía de tórax (fig. 1, superior) se objetiva un infiltrado en lóbulo superior derecho. La antigenuria de *Legionella pneumophila* y de neumococo eran negativas y se inicia tratamiento con amoxicilina/ácido clavulánico 875/125 mg/8 h.

Dos días después el paciente no mejora y acude a urgencias taquipneico con saturación basal de 88% que remonta con gafas nasales a 2 lpm hasta 95%, FC 46 lpm, tensión arterial 124/68 y roncus en campo pulmonar superior derecho.

En las pruebas complementarias se objetiva leucocitosis con neutrofilia, coagulopatía (INR 1,3) y proteína C reactiva de 103 mg/L y una nueva radiografía de tórax sin cambios. Se escala a ceftriaxona 2 g/24 h con levofloxacino 500 mg/24 h e ingresa en medicina interna.

Al tercer día de hospitalización presenta anisocoria pupilar con mayor midriasis del ojo izquierdo. Se realiza TAC craneal sin hallazgos intracraneales agudos. El test de colirios con pilocarpina muestra afectación del III par craneal izquierdo.

El angio-TAC craneal descarta lesión vascular y la resonancia magnética descarta patología del seno cavernoso, demostrando sinusitis maxilar derecha y quiste de retención etmoidal izquierdo (fig. 1, inferior). A las 24 h la anisocoria se resuelve espontáneamente.

Se realiza PCR múltiple en exudado nasofaríngeo y esputo que resulta positiva para *M. pneumoniae* y negativa para coronavirus, MERS-CoV, rinovirus/enterovirus, virus influenzae y parainfluenzae, metapneumovirus, adenovirus y virus respiratorio sincitial. También se obtiene positividad de la IgM frente a *M. pneumoniae* en suero. Las serologías frente a VIH, sífilis y virus hepatotropos son negativas. Se pauta azitromicina 500 mg/24 h durante 7 días.

A los 4 días consulta por pérdida de agudeza visual en ojo izquierdo. En la campimetría se objetiva pérdida difusa de la sensibilidad con defecto altitudinal superior en ojo izquierdo y agudeza visual de 0,5. La punción lumbar descarta infección del sistema nervioso central y con sospecha de neuritis óptica retrobulbar parainfecciosa se inicia corticoterapia con recuperación completa.

En revisiones posteriores, el electroencefalograma, la resonancia magnética de columna cervical y la angiorresonancia cerebral son normales y la punción lumbar de control no presenta bandas oligoclonales. Los anticuerpos en sangre antiacuaporina 4 y anticuerpos antiglucoproteína de la mielina de oligodendrocitos son