JOURNAL-BASED LEARNING EXERCISES

IBMS Institute of Biomedical Science Continuing Professional Development

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DEADLINE WEDNESDAY 3 JUNE 2020

Covert pathogenesis: transient exposures to microbes as triggers of disease.
Gilbert NM, Lewis AL. *PLoS Pathog* 2019 Mar 28; **15** (3): e1007586. doi: 10.1371/journal.ppat.1007586. eCollection 2019 Mar (https://doi.org/10.1371/journal.ppat.1007586). Assessment No: 030120

01	Covert pathogenesis is another term for polymicrobial infection.	**11**	The authors suggest that *G. vaginalis* is able to act as a covert pathogen to promote recurrent incidences of UTIs.
02	The authors suggest that in some cases transient microbial exposures may result in host responses resulting in disease after a microbe has been cleared.	**12**	Studies to date support the existence of a urinary microbiome.
03	A covert pathogen may reside in another bodily reservoir, which may allow for diagnostic opportunities.	**13**	Human recurrent UTI episodes are often caused by the same strain of *E. coli*.
04	A leading risk factor for UTIs is sexual activity but this is not thought to aid in the transfer of organisms to the urinary tract.	**14**	*G. vaginalis* is an infrequent member of the vaginal microbiome.
05	The covert pathogenesis model discussed in the paper could also be involved in reactivation of latent infections.	**15**	The authors' model of bladder exposure in mice to *G. vaginalis* resulted in exfoliation but did not result in neutrophils being detected in urine.
06	Covert pathogenesis as described in the paper does not refer to a situation whereby an organism can contribute to the severity of disease.	**16**	Women with bacterial vaginosis have lower rates of UTI than those with a lactobacilli-dominated vaginal microbiota.
07	The authors suggest that covert pathogenesis could be involved in some situations where standard culture techniques cannot locate high levels of a single organism.	**17**	It is believed that *E. coli* gains access to the urinary tract from nearby microbial niches.
08	The authors conclude that soluble toxins would not fall into the paradigm.	**18**	Bladder exposure to lactobacilli caused recurrent UTI and exfoliation in mouse models.
09	*Gardnerella vaginalis* has not been linked to symptomatic UTI.	**19**	Identification of covert pathogens in human disease is challenging due to the organisms not being present at the time of disease presentation.
10	Studies to date have not shown *Escherichia coli* capable of establishing latent infection in intracellular tissue reservoirs in the bladder.	**20**	An estimated 2% of women suffer more than six recurrent UTIs each year, equating to 70 million worldwide.

REFLECTIVE LEARNING

01 Given the thoughts detailed in the paper, reflect on whether there is a need to review those cases where standard culture techniques fail to find high levels of a single organism in cases presenting with clear urinary symptoms.

DEADLINE WEDNESDAY 3 JUNE 2020

Tissue staining for THSD7A in glomeruli correlates with serum antibodies in primary membranous nephropathy: a clinicopathological study. Sharma SG, Larsen CP. *Mod Pathol* 2018; **31** (4): 616–22 (www.ncbi.nlm.nih.gov/pmc/articles/PMC5908687/pdf/modpathol2017163a.pdf). Assessment No: 030520

01	THSD7A was detected in paraffin wax-embedded sections by immunoperoxidase staining using anti-THSD7A antibodies at a dilution of 1:80.	**11**	Membranous nephropathy is a pattern of glomerular immune complex disease with a variety of aetiologies.
02	Complete remission was defined as urinary protein excretion less than 0.3 g/d (uPCR <300 mg/g or 30 mg/mmol), confirmed by two values at least one week apart, accompanied by normal serum albumin and normal serum creatinine.	**12**	The identification of PLA2R as the antigenic target in most cases of primary membranous nephropathy has led to rapid changes in the area of treatment and diagnosis of the disease.
03	Membranous nephropathy is characterised by the renal biopsy finding of subepithelial immune-type deposits and the clinical presentation of nephrotic syndrome.	**13**	Cytoplasmic fluorescence of the transfected cells only at 1:10 dilution was considered to be positive.
04	THSD7A stain was interpreted as positive or negative. The stain was called positive if the staining was present in the granular pattern within the subepithelial side of the glomerular basement membranes.	**14**	Circulating autoantibodies to PLA2R and THSD7A were detected using indirect immunofluorescence assays. Each of the slides contained two different biochips in one incubation field. One biochip was coated with human embryonic kidney (HEK)293 cells that express the PLA2R or THSD7A protein, whereas the second biochip, which serves as a negative control, contained non-transfected HEK293 cells.
05	Low-titre THSD7A antibodies (1:10) at the time of diagnosis did not correlate with the level of proteinuria.	**15**	Among these 31 THSD7A-positive patients there were 12 males and 19 females. The mean age was 62 years (range 17–91 years).
06	Tissue staining for THSD7A is highly sensitive and specific for the detection of THSD7A-associated membranous nephropathy and it correlates strongly with serum positivity.	**16**	THSD7A-positive membranous nephropathy from December 2016 to June 2018 accessioned in our laboratory were selected for the study.
07	More data are needed to determine the clinical utility of similar testing for serum THSD7A antibody testing.	**17**	A total of 31 of the 131 membranous nephropathy cases diagnosed in the laboratory during the study period were positive for THSD7A.
08	The THSD7A antibody titre correlated with the level of proteinuria and was predictable of disease remission or response.	**18**	This male gender predominance seen in our cohort is different to that which is described in case series detailing PLA2R-associated membranous nephropathy.
09	Among the patients with known ethnicity (n=25) the disease was more common in Indians.	**19**	The PLA2R immunofluorescence staining procedure was performed as previously described on formalin-fixed, paraffin wax-embedded tissue.
10	The case series suggests that malignancy might be as common as previously reported in patients with THSD7A-associated membranous nephropathy.	**20**	The role of serum testing for anti-PLA2R antibody levels has become important in treating and monitoring the therapy of patients with PLA2R-associated membranous nephropathy.

REFLECTIVE LEARNING

01 Critically appraise the histological direct biopsy versus the indirect serological detection of THSD7A antibodies.

02 Discuss the relative frequency of PLA2R and THSD7A antibodies in idiopathic membranous nephropathy.