“Towards better clinicopathological diagnosis of lichen planus”

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Declarations

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision.

The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

I hereby certify that this thesis is submitted in the form of a series of published papers of which I am the first of more than two authors. I have included as a part of the thesis co-authorship declaration forms signed by all authors and endorsed by the Faculty Assistant Dean of Research Training, attesting to my contribution to the joint publications (attached in appendix).

Tania Day

Acknowledgements

Robert and I met on a boat from Greece to Turkey before I began medical school. He lived in Sydney, had a satisfying career, and knew it was impractical to begin a relationship with a young woman who was contractually required to spend the next 12 years studying, training, and working for the US government. Thankfully, he put pragmatism aside, immigrated to the USA, and never complained as we moved house four times in ten years. Our arrangement was that I would apply for my medical credentials to be recognized in Australia, and we would move there once my obligations were fulfilled in the USA. We spent the winter of 2011 in Sydney awaiting AHPRA registration, followed by a year of supervised practice at Maitland Hospital, before I was granted Fellowship with RANZCOG. After that, we traveled New South Wales looking for a town and a hospital to call home after so many years of itinerancy. Within a year of moving to Newcastle, we discussed the possibility of doing a PhD - a degree that might be described as supernumerary for a Senior Staff Specialist at a tertiary hospital. He encouraged me to do it if I thought it would be fulfilling or useful. For 20 years and counting, Robert's unwavering love, support, and optimism have been the bedrock of my life and career.

Lori Boardman ran the Colposcopy and Vulvar Clinics at Women and Infants' Hospital (WIH) of Rhode Island during the late 1990s and early 2000s, and was actively involved in research supported by Brown University and the National Institutes of Health. I am one of many WIH trainees whose careers would have been less rewarding had we not known Lori. During our rotation in her clinics, she provided us with a unique and important knowledge base in vulvovaginal and HPV-mediated disease, and inspired us to engage in research as an intellectual pursuit rather than a tick-box exercise. She guided me from planning to publication of two research projects during training, and provided a model for how to be an academic gynaecologist and compassionate leader. Her mentorship was transformative, and I am very grateful.

After training, I served four years in the US Navy, with tours in Okinawa, Japan, and Jacksonville, Florida. In both departments, I was the only gynaecologist with any formal training in vulvovaginal disease. Women referred with these issues were directed towards me and remained under my care while stationed at each site. It was rewarding to help women who often had been searching for a diagnosis and treatment plan for years. I remember that time fondly for the collegiality and interdepartmental collaboration that eased the transition from training to specialist practice.

The Maitland Hospital had a special clause in the full-time Staff Specialist position description to help attract and retain talent - one day a week could be spent pursuing a subspecialty interest of one's choice. Wanting to maximize this opportunity, I sought counsel from Felicity Park, who was working towards her Maternal-Fetal Medicine fellowship at the time. Felicity did her core training in Newcastle and is a visionary in her efforts to improve women's health in the Hunter region and beyond. Knowing my background and interests, she encouraged me to set up a vulval clinic at John Hunter Hospital. She took me on a tour of the facility and introduced me to departmental leadership. The clinic started by concentrating a trickle of referrals into a single session, but volume grew rapidly as local doctors heard about the service and saw positive results for their patients. Her encouragement and guidance were critical in transforming this idea into reality, and navigating the still unfamiliar bureaucracy of the Australian public health system.

Not long after the vulval clinic began, Jim Scurry called me to discuss a biopsy result. He asked if I had an interest in vulvovaginal disease, offered his help and mentorship, and gave me a copy of his book. We then ran some Clinicopathologic Correlation sessions and co-authored a case report on vulval pityriasis versicolour. He encouraged me to attend the 2013 International Society for the Study of Vulvovaginal Disease (ISSVD) meeting, where we discussed doing a research project so that I could qualify for ISSVD Fellowship. I soon recognised the incredible luck of this geographic circumstance - a world-renown vulval dermatopathologist was based in Newcastle because of family and lifestyle, and I had landed there for similar reasons with an

ambition to build an excellent clinical service in vulvovaginal disease. We started to meet once a week to review slides, discuss cases, and work on projects. Jim's tutelage has provided me with an understanding of vulvovaginal disease usually not accessible to gynaecologists, and his mentorship is foundational to this thesis and my career evolution.

Clinicopathologic research is only possible with the cooperation of clinicians who refer specimens to our Pathology department for expert assessment. The network of specialists who refer to Jim extends across New South Wales and Victoria, and most of these doctors are nationally or internationally recognized as experts in vulvovaginal disease. Their willingness to extract and share de-identified clinical data made this work possible. I am extremely thankful for their insights and editorial contributions, which have made the work richer and more applicable to the problems faced by busy clinicians. Likewise, our patients' willingness for their stories and photographs to be incorporated into research is commendable, as is their near-universal statement of hope that their experiences can improve the lives of other women.

While I was writing the manuscript on perianal disease, Felicity asked if I had considered doing a PhD by publication. Jim thought it an excellent idea and offered to be a supervisor. Pursuit of the degree while working full-time required the support of several departmental leaders. Professor Ian Symonds agreed to be the University supervisor, and has provided me with the practical advice and contacts so essential to progress through the degree requirements. Professor Henry Murray has consistently supported my academic pursuits, ensured I had administrative time, and always offered a smile as he signed off on multiple ethics applications. Carol Azzopardi, the Service Manager for Maternity and Gynaecology, has supported the development specialised clinics and my research efforts. Ken Jaaback and Geoff Otton, both Gynaecologic Oncologists, have also been invaluable to this work as referrers, educators, reliable sources of wisdom and encouragement, and co-authors. It has been a great privilege to work with so many inspiring people over the years, to be trusted by women to care for them, to know the generosity of genuine mentorship, and to hope to provide that gift to others.

List of publications included as part of the thesis

Day T, Holland S, Scurry J. Normal vulvar histology: variation by site. *Journal of Lower Genital Tract Disease* 2016;20(1):64-9.

Day T, Borbolla-Foster A, Phillips S, Pagano R, Dyall-Smith D, Scurry J, Garland SM. Can routine histopathology distinguish between vulvar cutaneous candidosis and dermatophytosis? *Journal of Lower Genital Tract Disease* 2016;20(3):267-71.

Day T, Knight V, Dyall-Smith D, Dennerstein G, Pagano R, Tran H, Tan Y, Yap D, Weigner J, Scurry J. The interpretation of non-diagnostic vulvar biopsies. *Journal of Lower Genital Tract Disease* 2018;22(1):74-81.

Day T, Bohl T, Scurry J. Perianal lichen dermatoses: a review of 60 cases. *Australasian Journal of Dermatology* 2016;57(3):210-15.

Day T, Burston K, Dennerstein G, Pagano R, Scurry J. Vestibulovaginal sclerosis versus lichen sclerosus. *International Journal of Gynecological Pathology* 2018;37(4):356-63.

Day T, Moore S, Bohl TJ, Scurry J. Cormorbid lichen planus and lichen sclerosus. *Journal of Lower Genital Tract Disease* 2017;21(3):204-8.

Day T, Weigner J, Scurry J. Classic and hypertrophic vulvar lichen planus. *Journal of Lower Genital Tract Disease* 2018;22(4):387-95.

Day T, Bowden N, Jaaback K, Otton G, Scurry J. Distinguishing erosive lichen planus from differentiated vulvar intraepithelial neoplasia. *Journal of Lower Genital Tract Disease* 2016;20(2):174-179.

Day T, Otton G, Jaaback K, Weigner J, Scurry J. Is vulvovaginal lichen planus associated with squamous cell carcinoma? *Journal of Lower Genital Tract Disease* 2018;22(2):159-165.

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Table of contents

1. Abbreviations

DEVIL	differentiated exophytic verruciform intraepithelial lesion
DIV	desquamative inflammatory vaginitis
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
dVIN	differentiated vulvar intraepithelial neoplasia
GVHD	graft-versus-host disease
H&E	hematoxylin and eosin
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
IHC	immunohistochemistry
-IN	intraepithelial neoplasia
ISSVD	International Society for the Study of Vulvovaginal Disease
LAST	Lower Anogenital Squamous Terminology
LP	lichen planus
LS	lichen sclerosus
LSC	lichen simplex chronicus
LSIL	low-grade intraepithelial neoplasia
MALT	mucosa-associated lymphoid tissue
MCJ	mucocutaneous junction
PAS	periodic acid-Schiff
PBI	patient benefit index
PCR	polymerase chain reaction
PCV	plasma cell vulvitis
PEH	pseudoepitheliomatous hyperplasia
QoL	quality of life
RCT	randomised controlled trial
SCC	squamous cell carcinoma
SIR	standardized incidence ratio
VAAD	vulvar acanthosis with altered differentiation
VAS	visual analog scale
VVC	vulvovaginal candidosis
VVS	vestibulovaginal sclerosis
uVIN	usual vulvar intraepithelial neoplasia

2. Abstract

Vulvovaginal lichen planus (LP) is a T-cell mediated inflammatory dermatosis characterised by quality of life impacts, irreversible anatomic changes, long-term treatment, and a reported increase in vulval cancer risk. Major knowledge gaps include that there are no consensus-based diagnostic criteria, no validated outcome measures, and little agreement on treatment strategies. The lack of diagnostic criteria produces a major limitation of clinical studies - not all participants have the disease of interest. Progress on diagnostic criteria is hindered by a lack of histopathologic research. The thesis aim was to address deficiencies in the clinicopathologic literature on vulvovaginal LP in order to lay the groundwork for international consensus guidelines on diagnosis.

Methodology for all studies was similar. The local pathology database was searched for diagnoses of interest. Slides were reviewed to select specimens meeting inclusion and exclusion criteria, then assessed for histopathologic features. Clinical notes and photographs were obtained from referring specialists. Clinical and histopathologic data were analysed together in an effort to describe patterns of presentation and diagnostic conundrums.

There are six key findings of the nine incorporated studies.

- Determination of anatomic site is fundamental to establishing a diagnosis.
- LP often presents with infectious and dermatologic comorbidities; identification requires liberal use of microbiology and biopsy at morphologically-distinct areas.
- There are two patterns of basal layer abnormality in erosive LP: the well-known degenerative pattern, and the newly described regenerative pattern.
- Non-recognition of the regenerative pattern contributes to the high non-diagnostic biopsy rate, along with clinician factors such as suboptimal biopsy timing or placement, and mistaking candidosis or vulvodynia for LP.
- Classic and hypertrophic LP have complex clinicopathologic appearances with multiple avenues for misdiagnosis.
- The evaluation of dermatosis-associated neoplasia requires an appreciation of all of the above components in order to avoid misattribution of vulvar cancers to LP.