



Original contribution

Structured analysis of histopathological characteristics of vulvar lichen sclerosis in a juvenile population[☆]



Beth Morrel MD^{a,b,*}, Patricia C. Ewing-Graham MBChB, FRCPath^c,
Irene A.M. van der Avoort MD PhD^d, Suzanne G.M.A. Pasmans MD PhD^b,
Jeffrey Damman MD PhD^{c,* **}

^a Erasmus MC, University Medical Center Rotterdam, Department of Obstetrics and Gynecology, 3015 GD Rotterdam, The Netherlands

^b Erasmus MC, University Medical Center Rotterdam-Sophia Children's Hospital, Department of Dermatology-Center of Pediatric Dermatology, 3015 GD, Rotterdam, The Netherlands

^c Erasmus MC, University Medical Center Rotterdam, Department of Pathology, 3015 GD Rotterdam, The Netherlands

^d Ikazia Hospital, Department of Obstetrics and Gynecology, 3083 AN, Rotterdam, The Netherlands

Received 22 July 2020; revised 9 September 2020; accepted 14 September 2020

Available online 21 September 2020

Keywords:

Lichen sclerosis;
Histopathology;
Vulva;
Pediatric;
Girls;
Juvenile vulvar lichen sclerosis

Summary Genital lichen sclerosis (LS), a chronic noninfectious dermatosis, is not rare in pediatric dermatology. The histopathological diagnosis in children and adults in both genital and nongenital LS is considered to be the same and encompasses a broad range of possible characteristics. Clinical manifestations and treatment options of genital LS in children are different depending on gender. The vast majority of boys are treated with circumcision, making for a larger amount of information on the histopathology of genital LS in boys, whereas substantial information on the histopathology of juvenile vulvar LS is lacking. In girls, vulvar LS almost always persists beyond puberty and, therefore, presents a particular challenge to clinicians and cause for concern for the patient. Vulvar LS in childhood and adolescence (juveniles) is underreported, and there are uncertainties with regard to the long-term course of the disease when it occurs at an age when the vulva is still developing. The present study investigates biopsies of 100 juvenile cases of vulvar LS and analyzes the presence or absence of the most salient histopathological characteristics of LS that are described in the literature.

Abbreviations: dVIN, differentiated vulvar intraepithelial neoplasia; HPV, Human papilloma virus; JVLS, Juvenile vulvar lichen sclerosis; LS, Lichen sclerosis; VLS, Vulvar lichen sclerosis; VSCC, Vulvar squamous cell carcinoma.

* Disclosures: None.

* Corresponding author. Department of Obstetrics and Gynecology, Erasmus MC, University Medical Center Rotterdam Dr. Molewaterplein 40,3015, GD, Rotterdam, The Netherlands,

** Corresponding author. Department of Pathology, Erasmus University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015, GD, Rotterdam, The Netherlands

E-mail addresses: b.morrel@erasmusmc.nl (B. Morrel), p.ewing@erasmusmc.nl (P.C. Ewing-Graham), iam.vd.avoort@ikazia.nl (I.A.M. van der Avoort), s.pasmans@erasmusmc.nl (S.G.M.A. Pasmans), j.damman@erasmusmc.nl (J. Damman).

<https://doi.org/10.1016/j.humpath.2020.09.003>

0046-8177/© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

We found that the range of histopathological characteristics known for adult LS are also present in juvenile vulvar LS, even at very young ages, including histopathological features associated with autoimmune disease, in support of the idea of a similar pathogenesis.

© 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Lichen sclerosus (LS) is a chronic cutaneous disease with a strong predilection for the genital and perianal skin, affecting women more often than men [1]. In children, the reverse might be the case, with boys being more often affected [2]. Unlike genital LS in boys, where the disease in the vast majority of cases is treated surgically [2] or in combination with steroids, this is not the case for girls. Vulvar LS (VLS) is a chronic remitting disease, treated topically with emollients and potent steroid ointments [3,4]. Steroids have been shown to be effective in prevention of progression of the disease in adults [5]. There is a need for lifelong treatment and follow-up.

VLS in females of any age is associated with pruritus, pain, dyspareunia and irreversible loss of vulvar architecture and in adult women is associated with a risk of developing vulvar squamous cell carcinoma (VSCC) [6]. An estimated 10–15% of the known subjects are children [7,8], with a prevalence in girls aged 2–16 years estimated to be at least 1:900 [9]. VLS that develops in childhood or adolescence is referred to as juvenile VLS (JVLS). The majority of juvenile cases will persist after puberty and beyond [10,11].

The etiology of LS is most likely multifactorial including autoimmune, genetic, and hormonal aspects as well as local factors including trauma and urine exposure [12]. A recent systematic review [13] suggests histopathology to be the gold standard for boys with genital LS and phimosis. The diagnosis of JVLS in girls is primarily based on clinical findings rather than on histopathology. Although VLS in adults gives a 12- to 15-fold increase in risk of developing VSCC [6], cases of VSCC younger than 18 years have not been reported [10]. Nor are there reports of juveniles with differentiated vulvar intraepithelial neoplasia (dVIN), the intermediary between VLS and VSCC and the presumed precursor of human papilloma virus–negative VSCC. Until more evidence is available, long-term or even lifelong surveillance is, therefore, advised [14].

When a biopsy is performed, the same histopathological criteria have been used for the diagnosis of LS in childhood or adolescence as in adulthood. This generally held consensus is largely based on two historical case series: the study by Clark and Muller [15] with 9 cases and the study by Laymon [16] with 3 cases. Several standard works describe the basic characteristics of the histopathology of VLS [17–19], of which the work of Regauer et al. [18] gives the most systematic approach. These sources describe a large number of histopathological features to be considered although no

single subset of these characteristics is regarded as necessary or sufficient for the diagnosis. Neither have these histological diagnostic criteria been used to delineate various stages of the disease nor have histological differences with regard to gender or age been analyzed [20]. The aim of the present study is to examine biopsies of JVLS using a uniform and semiquantitative methodology, with regard to the histopathological features known for adult LS, as described in the literature. These histopathological features associated with JVLS may give insights into the pathogenesis of this disease and might reveal more appropriate targets for treatment in these children.

2. Materials and methods

2.1. Materials

2.1.1. Defining the cohort of subjects to be studied

Approval from the institutional review board of our institution was obtained with regard to the study protocol.

Through PALGA, the Dutch Pathology Registry, the nationwide network and registry of all histopathology and cytopathology diagnoses in the Netherlands, a search was carried out to find all cases in the Netherlands registered as biopsy-proven VLS in the period from January 1991 through January 2015 for females up to 18 years of age. There were 328 cases thus identified. No identifiable data with regard to the subjects were shared with the research team. Date of biopsy, age at biopsy, the original conclusion of the pathologists and the name of the laboratory where the sample was originally analyzed were given.

2.1.2. Retrieving the material

For these anonymously identified cases, the hematoxylin and eosin (H&E)–stained slides or tissue samples, if slides were unavailable, were requested from the laboratories throughout the Netherlands. Material was, however, not always available. The slides or tissue samples from 137 subjects that were obtained from October 2018 through March 2019 were reanalyzed.

2.2. Methods

2.2.1. Standardization of tissue analysis for research purpose

PubMed was searched for publications on the histological characteristics of VLS. The flagship work of Regauer et al. [18] was taken as a starting point, augmented by histological features described by other authors

[17,19,21,22]. These histological characteristics of VLS described in the literature were grouped by skin layer, as per the work of Regauer et al. [18]. Items pertaining to histological findings for vessels, hair, sweat glands, and nerves as well as the presence of inflammatory cells were included. All characteristics are categorical and were grouped in three types of features based on how a tissue sample could be scored on that particular histological item. Scores may be a two-point nominal one: *yes, no* (eg, epidermal atrophy). Other items are scored on a four-point ordinal scale either as '*papillary dermis, superficial, mid-reticular, deep*' (eg, depth of homogenization) or as *absent, scant, moderate, profound* (eg, perivascular infiltrate). Finally, some items are scored on a four-point quantitative scale: *zero, 1, >1 up to 5, 5 or more* (eg, basal apoptotic keratinocytes). Judgment of the characteristic, as in daily practice, was carried out by first eyeballing the slide at low magnification and then studying the slide at high magnification. A total of 45 items were decided upon to be scored for each subject. A semiquantitative analysis of inflammatory cells, including lymphocytes, plasma cells, eosinophils, neutrophils, and histiocytes, was carried out. In addition, details with regard to nerves, blood vessels, and sweat glands were added. The scoring chart was set up (Excel) with discrete and limited choices per item, making it possible to analyze the specimens in a uniform fashion. The choice of characteristics and scoring was tested independently by two expert pathologists on a small number of samples. Their findings were subsequently discussed item by item to assure that the list would cover the spectrum of microscopic findings seen or to be expected. A complete list of the characteristics and the respective score on that item are shown in [Supplement 1](#).

2.2.2. Analysis of tissue samples

The two expert pathologists, a gynecopathologist (P.C.E.-G.) and a dermatopathologist (J.D.), together with the researcher (B.M.) simultaneously viewed all available slides of each case to judge the quality of the material and whether it was correctly registered as vulvar tissue with LS. This was carried out based on the descriptive methods used by pathologists in daily practice. If the sample displayed a combination of LS with another dermatological disorder such as a melanocytic nevus, it was excluded to assure that the characteristics seen were not attributable to any other dermatological condition [23]. If tissue samples but no slides were sent, or if slides proved to be of poor quality owing to fading and availability of a tissue block, new H&E slides were made.

Of the 137 subjects for which material was analyzed, for 16 cases, the material was of too poor quality or the diagnosis was uncertain; in 7 cases, the diagnosis of VLS was rejected because the findings were deemed not specific; 8 had been mistakenly coded as vulva; and there were 6 cases of a melanocytic nevus combined with the LS. This resulted in 100 cases of confirmed VLS comprising the study group.

For the 100 samples that met the aforementioned inclusion criteria, the pathologists continued with a complete detailed systematic analysis as described previously in Section 2.2.1, scoring the sample on the 45 characteristics ([Supplement 1](#)). Discrepancies were discussed until a consensus was reached. At each session, about 10–15 cases were analyzed and recorded in the spreadsheet.

Descriptive statistics were generated using the statistical package SPSS (IBM SPSS 25) with regard to population characteristics and the histological findings.

3. Results

The cohort of potential subjects are those 328 females aged 18 years or younger at the time of biopsy who underwent a vulvar biopsy registered as showing VLS during the course of 25 years, January 1991–January 2015. Tissue samples from 137 subjects were obtained, which represents 42% of the entire cohort. After exclusions as described in Section 2.2.2, 100 cases remained and were included to comprise the study population, for which the material was analyzed based on protocol.

3.1. Study population compared with the cohort

To rule out inherent bias, the population characteristics for the entire cohort of 328 subjects were compared with those of the study group of 100 confirmed cases with respect to year of biopsy and age at biopsy.

The distribution of the year of biopsy ([Fig. 1A](#)) is similar in the entire cohort to that of the 100 subjects studied in depth ([Fig. 1B](#)). The chi-square test showed no significant difference in the year of biopsy between the total cohort population and study group ($P = 0.54$). We note that despite the fact that in the literature, experts currently emphasize that VLS in children is primarily a clinical diagnosis and histology is usually not necessary, we found that the number of biopsies taken in the Netherlands has not diminished in the course of 25 years ([Fig. 1A](#)).

Age at biopsy for the cohort and the study group is given in [Fig. 1C](#) and [D](#). In both groups, there is a peak in prepuberty. For girls in the study group up to 12 years old, the average age was 7.05 years, similar to what is described in the literature, that is, 6.7 years at the time of diagnosis. The chi-square test showed no significant difference in age at biopsy between the cohort and study group ($P = 0.22$).

3.2. Histological characteristics found in JVLS

The 100 cases of histologically confirmed VLS on revision by our group comprised the study group, for which an analysis of 45 histopathological characteristics was performed. There was a wide range of findings from histopathological features that might suggest very active disease to features suggesting completely extinguished disease, even despite the very young age of many of the subjects. The findings are

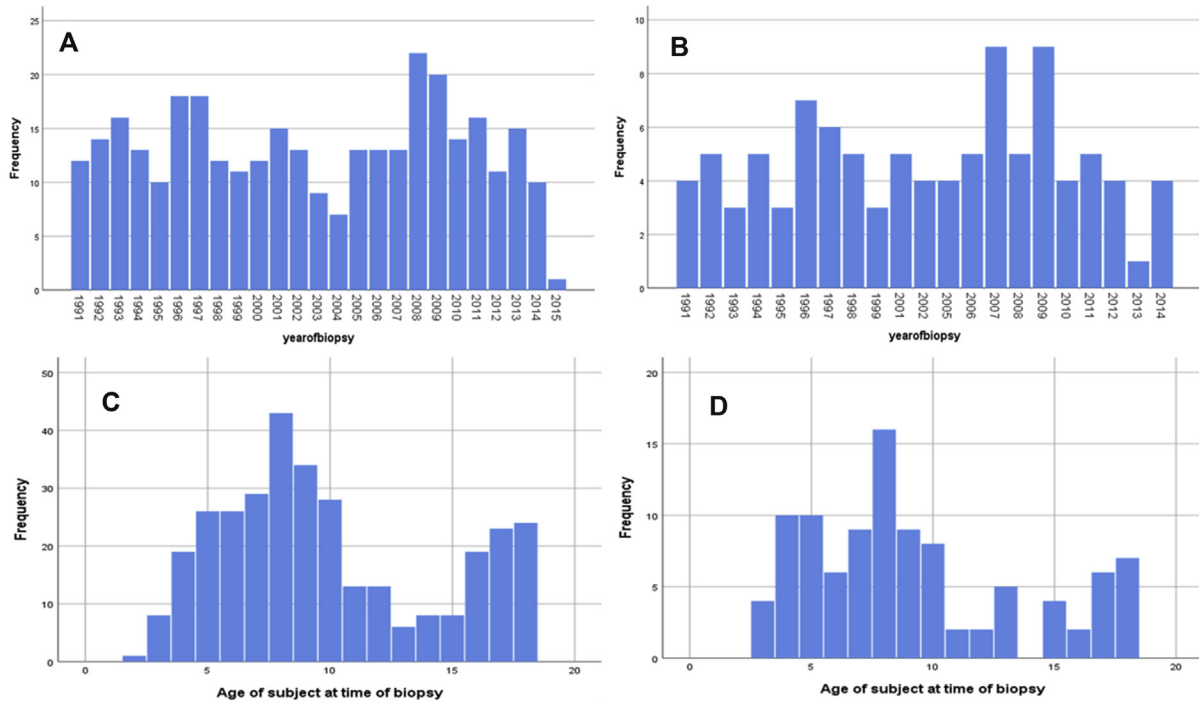


Fig. 1 Comparison of the population (328 subjects) to the study group (100 subjects) for year and age at biopsy. A, Year of biopsy of the population; B, year of biopsy of the study group; C, age at biopsy of the population; D, age at biopsy of the study group.

discussed in the following section by skin layer, adnexal structure, and cell type, and the results for the most prominent characteristics are summarized in Fig. 2. The findings often included classic features of VLS, as seen in Fig. 3A.

3.2.1. Epidermis

In most cases, the following characteristics were seen: hyperkeratosis (96%), basal vacuolization of keratinocytes (88%), as shown in Fig. 3B, and lymphocytic exocytosis (91%), although usually only scant to moderate. Epidermal atrophy, seen in 50% of the cases, was not significantly related to the age of the subject, when evaluated using the

chi-square-test ($P = 0.77$). Epidermal atrophy in an 8-year-old girl is shown in Fig. 3A. Basal apoptotic keratinocytes were seen in 47% of cases, although usually less than 5 per low-power field. In addition, acanthosis was seen in 43% of cases. A number of characteristics in the epidermis were infrequently seen: spongiosis (14%), high apoptotic cells (12%), and basal squamatization (9%). In addition, basement membrane thickening appeared in 8% of cases. Several characteristics were very rarely or never seen: obscured interface (2%), psoriasiform hyperplasia (3%), and vertical columns of parakeratosis (0%).

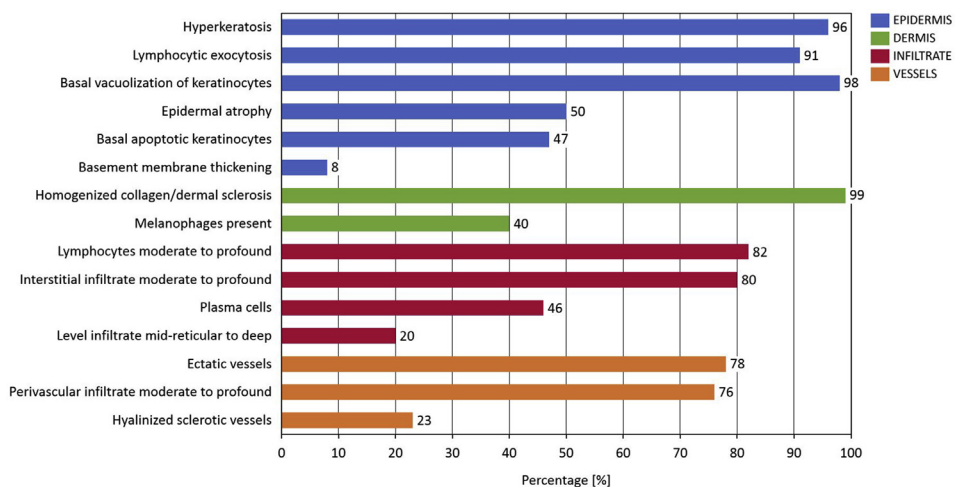


Fig. 2 Occurrence of histopathological features in juvenile vulvar lichen sclerosis (JVLS).

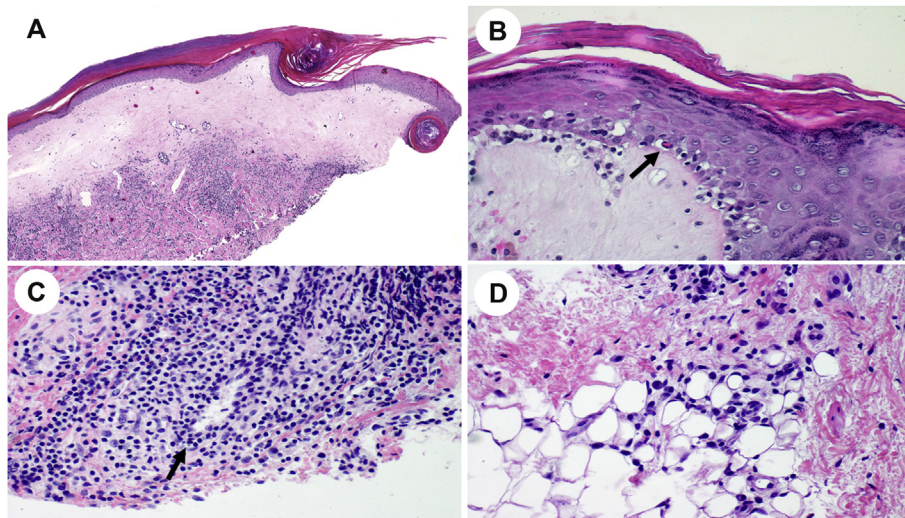


Fig. 3 Histopathological features seen in JVLS. A, Classic vulvar lichen sclerosis (8-year-old child) showing classical features of epidermal atrophy with orthokeratotic plugging, dermal sclerosis, and a band of lymphoid cells; B, vacuolar interface dermatitis (3-year-old child) with cell-poor vacuolar degeneration, prominent basal vacuolization, and few apoptotic cells (arrow); C, lymphocytic vasculopathy (9-year-old child) showing a dense perivascular lymphocytic infiltrate with the transmural influx of lymphocytes (arrow), nuclear debris, and edematous thickening of the vessel wall; D, deep plasma cells (5-year-old child) illustrating deep lymphoplasmacytic infiltrate at the level of the deep dermis and subcutaneous fat. JVLS, juvenile vulvar lichen sclerosis.

3.2.2. Dermis

In all, 99% cases showed dermal sclerosis; of which in most cases (98%), the homogenization was in the papillary dermis or superficial reticular dermis. Papillary edema was found in 29% of cases, and in 40% of the cases, melanophages were observed.

3.2.3. Infiltrate

The level of infiltrate was at least superficial. In only one case was the infiltrate limited to the papillary dermis, and in 20% of cases, the infiltrate was mid-reticular to deep. Interstitial infiltrate was moderate to profound in 80% of cases. A perivascular infiltrate was always seen, with 76% of cases being moderate to profound, as shown in Fig. 3C. Lichenoid infiltrate was seen in only one case. Lymphocytes were always present, and in 82% of cases, they were moderate to profound. Plasma cells were present in 46% of the cases, although usually scant (35%) and sometimes deep (Fig. 3D). The findings on eosinophils were similar, being present in 37% of the cases, although scant. Neutrophils were less common (14% of cases). And finally, histiocytes were always present (100%), although usually scant (79% of cases).

3.2.4. Vessels

The number of vessels was generally normal (88%), in 11% of cases, this amount showed an increase. Ectatic vessels were seen in 78% of cases. Hyalinized/sclerotic vessels, on the other hand, were seen in 23% of cases, and a lymphocytic vasculitis was seen in just 13% of cases (Fig. 3C).

3.2.5. Hair

Hair follicles were seen in 71 cases. Of these, 58 (82%) cases had perifollicular dermatitis, as seen in Fig. 4A, and

in 59 (83%) cases, lymphocytic exocytosis was seen at the hair follicle, although almost always scant to moderate. Basal vacuolization of keratinocytes at the hair follicle was seen in 50 cases (70%). In addition, 35 (49%) cases showed hypergranulosis, follicular hyperkeratosis, or plugging, and 26 (37%) cases demonstrated basal apoptotic keratinocytes (Fig. 4B–C); of which, the majority were categorized as moderate to profound. On the other hand, 7 (10%) cases had follicular acanthosis and 13 (18%) had basal membrane thickening at the hair follicle. Just one case had dystrophic hair shafts, and one case showed an obscured interface.

3.2.6. Sweat glands

Sweat glands were able to be judged in 69 cases. The only characteristic scored for sweat glands that was seen in a substantial number of cases was the influx of lymphocytes into the sweat gland epithelium (lymphocytic syringotropism), which is seen in 16 cases (23%). Acrosyringal acanthosis was seen once, both acrosyringal hyperkeratosis/hypergranulosis and the influx of neutrophils (neutrophilic syringotropism) into the sweat gland epithelium were seen twice, and basal membrane thickening was seen three times.

3.2.7. Nerves

Nerves were seen in 88 of the cases, in 5 of which (6%) a perineural lymphocytic inflammation was observed (Fig. 5).

3.3. Comparison before and after puberty

Because clinical information was not available, age more than 12 years was used as a proxy for puberty. There

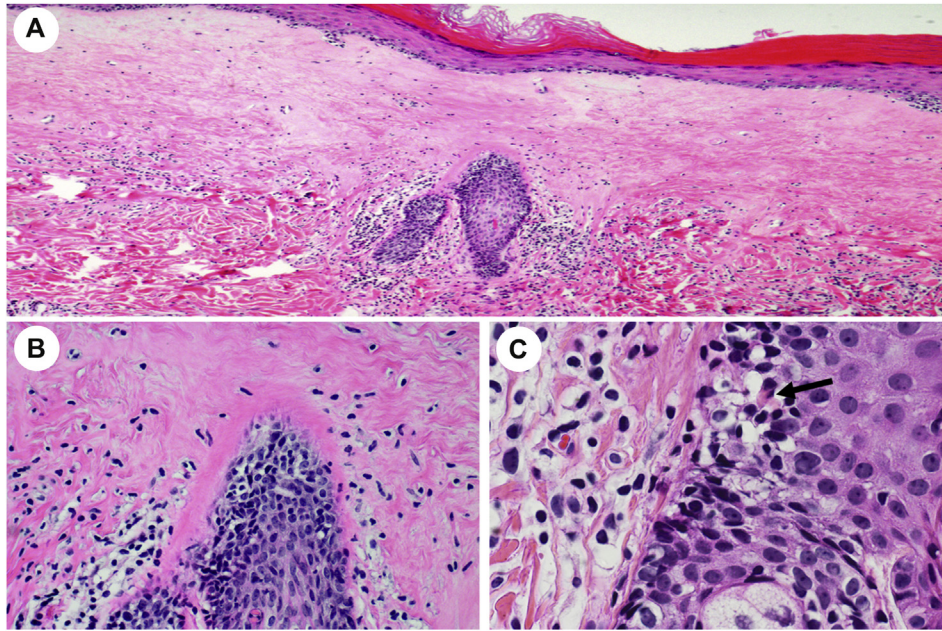


Fig. 4 Perfollicular dermatitis and vacuolar interface dermatitis affecting the follicular epithelium (6-year-old child). A, Classic changes of lichen sclerosis can be seen with perfollicular dermatitis; B, perfollicular dermatitis affecting the hair follicle itself; C, higher magnification showing vacuolar degeneration and apoptosis (arrow).

were 76 subjects who were 12 years or younger and 24 subjects who were older than 12 years. Statistical differences by age more than and less than 12 years were analyzed using the chi-square test.

3.3.1. Differences in histopathology in those older than 12 years of age

Statistically significant differences were seen for just three of the characteristics analyzed. Lymphocytic exocytosis of the epidermis was moderate in 32.9% of the prepubertal and in 50% of the postpubertal subjects ($P = 0.05$). Melanophages in the dermis were more often

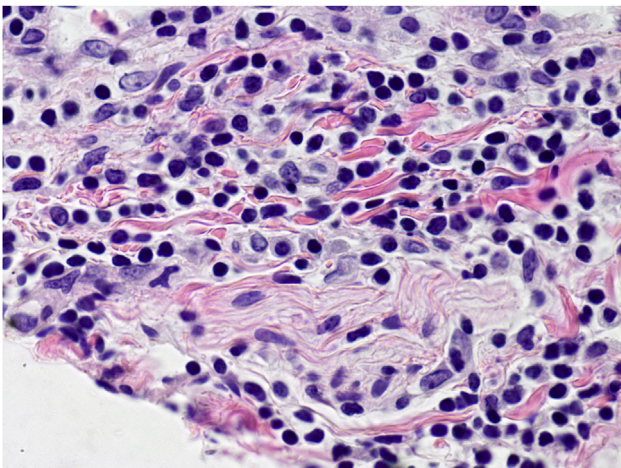


Fig. 5 Perineural lymphocytic inflammation (9-year-old child) showing concentric perineural inflammation with lymphocytes adjacent to a small nerve.

present in biopsies after puberty (32.9% versus 62.5%; $P = 0.01$). Hyalinized sclerotic vessels were present in 15.8% of the younger subjects and in 45.8% of the girls older than 12 years ($P = 0.02$).

3.3.2. Differences in the presence of adnexa in those older than 12 years of age

Regarding the presence of hair follicles, there was a significant difference depending on the age-group, 78.9% of the biopsies of prepubertal subjects showed hair follicles, whereas 54.2% was the case in postpubertal subjects ($P = 0.017$). Sweat glands were significantly more often present in the biopsies before puberty than after puberty (77.6% vs. 41.7%; $P = 0.001$). There was no difference by age-group as to whether nerves were seen ($P = 0.93$). The presence of hair and sweat glands seen more often in the biopsies of younger subjects may be due to the dimensions of the labia minora of the prepubertal child, making it more likely to include hair-bearing skin when taking a vulvar biopsy.

3.4. Summary of the results

In summary, the findings (Fig. 2) are as follows. Hyperkeratosis, homogenized collagen/dermal sclerosis, and vacuolar basal vacuolization of keratinocytes in the epidermis are nearly always present, whereas epidermal atrophy was found in half of the cases. A moderate to profound perivascular infiltrate and ectatic vessels were seen in three-quarters of the subjects. Regarding the adnexa, analysis of hair follicles showed perfollicular dermatitis in more than half of the cases and follicular

plugging in a third of cases. Nerves and sweat glands were often seen; however, a minority of cases displayed specific changes attributable to VLS. The interstitial infiltrate, seen in most cases, was moderate to profound 80% of the time, although it was superficial in the majority of cases. Most histopathological features scored do not statistically differ when comparing before or after puberty. Hair follicles and sweat glands are more likely to be present in the biopsies of prepubertal subjects. A complete list of the results is given in [Supplement 2](#).

4. Discussion

The aim of this study is to investigate the histopathology of JVLS, a subject on which to date there are only small case series. Material was studied from an historical cohort of all juvenile girls in the Netherlands who underwent vulvar biopsies that were originally classified as VLS over the course of 25 years. The study systematically investigates the histopathological characteristics attributed to VLS in 100 juvenile girls, looking at to what extent known features of adult VLS are seen in this age-group. The full range of possible histopathological criteria known for adult LS was analyzed and shown to be present.

The present study is the first large series studying the histopathology of JVLS. Using a standardized and semi-quantitative approach, it was shown that the same characteristics as described for adult VLS in the literature [18] are found in JVLS, with broad variation between cases and regardless of pubertal status. The most common histopathological features that were found in JVLS were similar to adult LS and included epidermal atrophy, vacuolar interface dermatitis, dermal homogenization, and hyalinized vessels. Other less frequent findings were lymphocytic vasculitis/vasculopathy and perineural dermatitis. Interestingly, one additional frequent finding, which is not well documented in the literature in the setting of LS, is the periappendageal and, in particular, perifollicular dermatitis. Thus, the present study is the first substantial study on the histopathology of JVLS and confirms the assumption previously based on a few small case series that the histopathology of JVLS concurs with that of adult VLS and demonstrates the broad range of possible histopathological manifestations of the disease across a large cohort.

The methodology used was more extensive than formerly applied in the study of LS. Previous studies use the systematic approach of Regauer et al. [18] to describe the presence and absence of certain features without quantifying the degree to which characteristics are present. The seminal publication of Regauer et al. [18] reported that in early LS, changes of the hair unit such as basement membrane thickening, appendageal hyperkeratosis, and hypergranulosis may be observed before the interfollicular epidermis shows characteristic features of LS, but they did

not describe perifollicular inflammation. In a study by Knio et al. [24], skin biopsies were analyzed in a heterogeneous group of 60 subjects with LS, with the median age being 47 years (range = 6–80), of which 16 were genital, using the criteria of Regauer et al. [18]. In contrast to Regauer et al. [18], Knio et al. [24] also found perifollicular inflammation in 20% of the cases. In the present study, perifollicular dermatitis was seen in 58 cases (82% of cases, when hair follicles were present), and keratinocyte apoptosis/necrosis of hair follicles was seen in 36 cases (50%, if hair was present). Other studies [21,25] have used the systematic approach of Regauer et al. [18] in adult populations to differentiate VLS from other dermatological diseases. Studies are needed to further elucidate and specify which histopathological characteristics found in LS may aid in differential diagnostics. The present study quantifies the presence and degree of histopathological features associated with this disease, which can be used in both clinical practice and research.

In this study of JVLS, the histopathological features often associated with autoimmune disease are shown to be present in a large number of cases. Most of the histopathological features found in LS, including characteristics such as vacuolar interface dermatitis, periadnexal dermatitis, lymphocytic vasculitis/vasculopathy, and perineural dermatitis, as well as our observations of profound perifollicular dermatitis, have also been described in collagen vascular diseases [26,27] (such as lupus erythematosus) and are in support of the presumptive autoimmune basis for VLS. Whether the degree of perifollicular dermatitis is more profound in JVLS than in adult LS remains to be investigated. The follicular involvement seen, with keratinocyte necrosis/apoptosis, is also a common feature of connective tissue diseases [26]. Immunohistochemical studies [28] support the immunopathological etiology of LS. This is in line with current views on VLS, especially in girls, wherein the available data on immunopathology are primarily given by family history and serological parameters [29–31]. The role of autoimmunity in males is much less clear [32]. The findings in the present study give histological data in support of the concept of an immunological basis of JVLS.

It should be noted that in the present study, no cases of dysplasia or suspicion of a premalignant lesion such as dVIN were seen. Population studies [33,34] show that developing VLS at a young age increases the risk of developing a VSCC. However, how this should be interpreted specifically with regard to the prognosis for children suffering from JVLS is yet to be elucidated.

A possible weakness of this study is that cases that were biopsied may possibly represent a bias toward clinically uncertain, more severe, or therapy-resistant cases. In addition, owing to anonymity, the findings cannot be correlated to clinical parameters such as signs and symptoms or progression of the disease. The strengths of the present study include the following. The histological analysis has been

carried out in a standardized and systematic manner, looking in depth at which histological features known for VLS were present. The study group includes 42% of the entire cohort, without an inherent bias (Section 3.1.1). In addition, observer bias was reduced by having two expert pathologists simultaneously study the material. The method used provides pathologists and clinicians with an instrument to aid in clinical practice by using this systematic approach in diagnostics of diagnostically difficult or complex cases [21]. Although somewhat more time-consuming for day-to-day clinical practice, by providing a reproducible scoring method, opportunity is created for research purposes to help elucidate the clinical implications of various histopathological characteristics, for example, perineural infiltrate. In addition, the method has the potential to be a tool to assess therapy results in trials as well as to analyze and compare different demographic groups (males/females, juveniles/adults, those who develop carcinoma, and those who do not). In line with the goals of the Lichen Sclerosus Priority Setting Partnership [35], this could ultimately help to advance insight into VLS and JVLS, in particular. Future plans include correlating the histological findings with the clinical course of the disease. A study is now underway to trace these women, of whom at present, more than 90% have reached adulthood, to analyze the course of their disease, including any treatment they have undergone or complications they may have experienced, and, if possible, to correlate this to the histopathological information from their childhood biopsies.

5. Conclusions

In the present study, using systematic and semi-quantitative methods, the findings for a series of 100 cases confirm that the histopathology of VLS in juveniles encompasses the entire range of features attributed to VLS in general. This includes the presence of histopathological features associated with autoimmune disease. We propose that studies applying a systematic histopathological analysis may aid in further clinical research on a number of topics including the pathophysiology of JVLS, new (systemic) therapy modalities, and differences in demographic subgroups suffering from LS and in correlating specific histological findings with clinical information.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.humpath.2020.09.003>.

Acknowledgments

The authors thank Shatavisha Dasgupta MD, for her help with digitalizing the slides and producing the illustrations, and Rinus (Q.J.M.) Voorham, Engr. PhD, research coordinator of

the PALGA Institute, for carrying out the search in the PALGA database and his support in retrieving the material.

References

- [1] Tasker GL, Wojnarowska F. Lichen sclerosus. *Clin Exp Dermatol* 2003;28:128–33.
- [2] Balakirski G, Grothaus J, Altengarten J, Ott H. Paediatric lichen sclerosus: a systematic review of 4516 cases. *Br J Dermatol* 2020; 182:231–3.
- [3] Becker K. Lichen sclerosus in boys. *Dtsch Arztebl Int* 2011;108: 53–8.
- [4] Ellis E, Fischer G. Prepubertal-onset vulvar lichen sclerosus: the importance of maintenance therapy in long-term outcomes. *Pediatr Dermatol* 2015;32:461–7.
- [5] Lee A, Bradford J, Fischer G. Long-term management of adult vulvar lichen sclerosus: a prospective cohort study of 507 women. *JAMA Dermatol* 2015;151:1061–7.
- [6] van de Nieuwenhof HP, van der Avoort IA, de Hullu JA. Review of squamous premalignant vulvar lesions. *Crit Rev Oncol Hematol* 2008;68:131–56.
- [7] Sahn EE, Bluestein EL, Oliva S. Familial lichen sclerosus et atrophicus in childhood. *Pediatr Dermatol* 1994;11:160–3.
- [8] Smith SD, Fischer G. Paediatric vulval lichen sclerosus. *Australas J Dermatol* 2009;50:243–8.
- [9] Powell J, Wojnarowska F. Childhood vulvar lichen sclerosus: an increasingly common problem. *J Am Acad Dermatol* 2001;44:803–6.
- [10] Morrel B, van Eersel R, Burger CW, et al. The long-term clinical consequences of juvenile vulvar lichen sclerosus: a systematic review. *J Am Acad Dermatol* 2020;82:469–77.
- [11] Lagerstedt M, Karvinen K, Joki-Erkkila M, Huotari-Orava R, Snellman E, Laasanen SL. Childhood lichen sclerosus—a challenge for clinicians. *Pediatr Dermatol* 2013;30:444–50.
- [12] Powell JJ, Wojnarowska F. Lichen sclerosus. *Lancet* 1999;353: 1777–83.
- [13] Li J, Deng C, Peng Q. Underestimation of genital lichen sclerosus incidence in boys with phimosis: results from a systematic review. *Pediatr Surg Int* 2018;34:1245–50.
- [14] Nerantzoulis I, Grigoriadis T, Michala L. Genital lichen sclerosus in childhood and adolescence—a retrospective case series of 15 patients: early diagnosis is crucial to avoid long-term sequelae. *Eur J Pediatr* 2017;176:1429–32.
- [15] Clark JA, Muller SA. Lichen sclerosus et atrophicus in children. A report of 24 cases. *Arch Dermatol* 1967;95:476–82.
- [16] Laymon CW. Lichen sclerosus et atrophicus in childhood. *Arch Dermatol Syphilol* 1945;52:351–3.
- [17] Hewitt J. Histologic criteria for lichen sclerosus of the vulva. *J Reprod Med* 1986;31:781–7.
- [18] Regauer S, Liegl B, Reich O. Early vulvar lichen sclerosus: a histopathological challenge. *Histopathology* 2005;47:340–7.
- [19] Kurman RJ, Ellenson LH, Ronnett BM. Blaustein's pathology of the female genital tract. Boston, MA: Springer US; 2011.
- [20] Tran DA, Tan X, Macri CJ, Goldstein AT, Fu SW. Lichen Sclerosus: an autoimmunopathogenic and genomic enigma with emerging genetic and immune targets. *Int J Biol Sci* 2019;15:1429–39.
- [21] Fung MA, LeBoit PE. Light microscopic criteria for the diagnosis of early vulvar lichen sclerosus: a comparison with lichen planus. *Am J Surg Pathol* 1998;22:473–8.
- [22] Weyers W. Hypertrophic lichen sclerosus sine sclerosis: clues to histopathologic diagnosis when presenting as psoriasiform lichenoid dermatitis. *J Cutan Pathol* 2015;42:118–29.
- [23] Pinto A, McLaren SH, Poppas DP, Magro CM. Genital melanocytic nevus arising in a background of lichen sclerosus in a 7-year-old female: the diagnostic pitfall with malignant melanoma. A literature review. *Am J Dermatopathol* 2012;34:838–43.

- [24] Knio Z, Kurban M, Abbas O. Lichen sclerosis: clinicopathological study of 60 cases from Lebanon. *Int J Dermatol* 2016;55:1076–81.
- [25] Niamh L, Naveen S, Hazel B. Diagnosis of vulval inflammatory dermatoses: a pathological study with clinical correlation. *Int J Gynecol Pathol* 2009;28:554–8.
- [26] Calonje E, McKee PH. McKee's pathology of the skin. Edinburgh: Elsevier, Saunders; 2012.
- [27] Regauer S, Liegl B, Reich O, Beham-Schmid C. Vasculitis in lichen sclerosis: an under recognized feature? *Histopathology* 2004;45:237–44.
- [28] Farrell AM, Marren P, Dean D, Wojnarowska F. Lichen sclerosis: evidence that immunological changes occur at all levels of the skin. *Br J Dermatol* 1999;140:1087–92.
- [29] Lee A, Fischer G. Diagnosis and treatment of vulvar lichen sclerosis: an update for dermatologists. *Am J Clin Dermatol* 2018;19:695–706.
- [30] Powell J, Wojnarowska F, Winsey S, Marren P, Welsh K. Lichen sclerosis premenarche: autoimmunity and immunogenetics. *Br J Dermatol* 2000;142:481–4.
- [31] Cooper SM, Ali I, Baldo M, Wojnarowska F. The association of lichen sclerosis and erosive lichen planus of the vulva with autoimmune disease: a case-control study. *Arch Dermatol* 2008;144:1432–5.
- [32] Kreuter A, Kryvosheyeva Y, Terras S, et al. Association of autoimmune diseases with lichen sclerosis in 532 male and female patients. *Acta Derm Venereol* 2013;93:238–41.
- [33] Bleeker MC, Visser PJ, Overbeek LI, van Beurden M, Berkhof J. Lichen sclerosis: incidence and risk of vulvar squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 2016;25:1224–30.
- [34] Halonen P, Jakobsson M, Heikinheimo O, Riska A, Gissler M, Pukkala E. Lichen sclerosis and risk of cancer. *Int J Canc* 2017;140:1998–2002.
- [35] Simpson RC, Cooper SM, Kirtschig G, et al. Lichen sclerosis priority setting partnership steering G. Future research priorities for lichen sclerosis - results of a James Lind alliance priority setting partnership. *Br J Dermatol* 2019;180:1236–7.