Verrucae pedis in children with Juvenile Idiopathic Arthritis and other paediatric rheumatic diseases: a cross-sectional study.

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Research Article

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Abstract

Background

Verrucae pedis (VPs) are a common viral infection of the skin seen in children. There are limited studies of the prevalence, duration and impact of VPs in children who are immunosuppressed. The studies available suggest that, in these children, the warts are more widespread and are more long-standing. The primary aim of this study was to determine the prevalence of VPs in children attending rheumatology clinics who may have some degree of immunosuppression due to their prescribed medication and compare this to the reported prevalence in the healthy population.

Method

Children attending out-patient rheumatology appointments who had a paediatric rheumatology consultant named as the lead clinician, were recruited. The young people were aged between four and 17 years old. A visual inspection of both feet was used to identify potential VPs. Diagnosis of a VP was confirmed on observation of the typical clinical features of a VP. The location, duration of presence, previous treatments, presence of VPs in other family members and psychological impact was recorded.

Results

A total of 71 children were included. Of the group, 55 children had no VPs present, 16 children had one or more VPs. The prevalence of VPs was 22.5%. Medication impacting on the immune system was prescribed in 80% of the group. There appeared to be no greater chance of having VPs if taking immunosuppressive medication than compared to having no medication (OR = 1.1, 95%CI 0.26 to 4.48, p = 0.46). Children with VPs tended to be 9 years old or older with few children in the older age range (13–17 yrs) having VPs suggesting that most VPs do resolve by the teenage years. In total, 37.5% of the young people with VPs had lesions that had been present for 24 months or more. Two-thirds of the subjects were not concerned about VPs being present and most subjects with a VP did not know what it was, but despite this the majority of subjects (81%) had sought treatment for the VPs.

Conclusion

Children with JIA and other rheumatic conditions have no greater prevalence of VPs compared to the general population. The VPs present were of a similar clinical type and did not seem to be more widespread or unusual as has been reported in other immunocompromised populations. The percentage of lesions remaining beyond 24 months was found to be slightly greater than has been reported in other healthy populations. The children in this study seemed to be less concerned psychologically about their VPs, despite this most families had sought treatment for the verrucae.

Background

Verrucae pedis (VP) (plantar warts) are a common viral infection of the skin that leads to the formation of benign, hyperkeratotic papillomas. Caused by the human papilloma virus (HPV), they are most prevalent in children, with a Dutch study suggesting that foot and hand warts had a prevalence of 33% in children aged 4–12 years, with 70% of these being plantar warts [1]. The study identified that warts tended towards natural resolution, with half the group being clear of warts after one year, agreeing with the findings of previous study [2]. Younger children and those with non-Caucasian skin showed the highest resolution rates. In contrast, in young adults, the prevalence is much lower with a large Chinese study identifying hand (common) and plantar warts as having a prevalence of 1.4%; half of all warts also resolved after one year [3].

Although over 120 HPV types have been identified, plantar verrucae are usually from HPV types 1, 2, 4, 27 and 57 in healthy children and young adults [3, 4, 5]. A study focusing on plantar warts and their relation to demographic and clinical characteristics of 72 patients (including adults) found that the most prevalent genotypes detected among the 105 plantar warts were HPV-57 (37.1%), HPV-27 (23.8%), HPV-1a (20.9%), HPV-2 (15.2%) but a small percentage (2.8%) also had HPV-65 [6]. Most patients (78%) presented with a single plantar wart. It is not uncommon to find multiple HPV types in a single wart [5, 7].

The data for healthy children suggests that, in general, verrucae pedis (VP) infection is a mild, self-limiting problem. However, one study reported that nearly 30% of their group considered the warts inconvenient with problems such as pain, irritation and having an unsightly appearance; 38% of the group had attempted treatment of the warts [1]. An earlier study by Ciconte *et al* [8] identified that plantar warts had similar mean values for psychological morbidity as hand warts. Warts on the hands had higher scores for measures such as "*other people's view of the lesions*", but plantar warts had greater scores for measures such as frustration with persistence, pain and impact on activities. Sterling *et al* [9] identified warts as being cosmetically unappealing, painful and irritating with a further study [10] additionally noting that they cause embarrassment. A recent medical phone-in on the BBC radio featured people reporting that they felt "*humiliated*" when people saw their verrucae and that the verrucae caused "*real misery*". No study to date has been found that identified the psychological impact of having plantar warts in immunosuppressed patients compared with healthy subjects.

The data on the resolution of warts for children who are immunocompromised is less clear. It is apparent that primary immunodeficiency diseases are associated with increased HPV infections [11], and the lesions tend to be more widespread and unusual compared to the lesions seen on the feet of healthy children. In a study of VPs in adult subjects with a positive and negative HIV (human immunodeficiency virus) status, the same four HPV types were identified regardless of HIV status [12]. An earlier study on VPs and HIV found that the plantar warts were larger and more numerous when the subject was HIV positive [13]. All subjects in these trials were adults. More recent studies on immunocompetent and immunocompromised subjects agreed that the same HPV types are found in these populations and

otherwise healthy populations [14, 15] but it is still unclear whether the number of HPV types per lesion may differ between immunocompetent and compromised subjects [16].

Studies on immunocompromised children are of low evidence case reports. Marini *et al* [17] reported on nine-year-old twin sisters who presented with long-standing severe plantar warts following bone marrow transplantation for severe combined immunodeficiency (SCID). The wart was not HPV typed. Although not referenced, the authors suggest that the prevalence of HPV infection in immunodeficiencies is as high as 40–60% and agree with the picture of typical persistence of the infection rather than the natural history of spontaneous regression, and thus these children will be troubled for longer by lesions that may well be painful and that they also consider unsightly or embarrassing.

Paediatric rheumatic diseases include a group of conditions where autoimmune or autoinflammatory diseases occur. Juvenile Idiopathic Arthritis is the most common rheumatic disease of childhood [18]. It is an autoimmune disease whereby antibodies to the body's synovial structures are generated resulting in joint and soft tissue inflammation. Other conditions include Systemic Lupus Erythematosus and Juvenile Dermatomyositis. In order to suppress or alter the autoimmune reaction, the majority of children are placed on immunosuppressive medication such as methotrexate, and those with more severe disease receive biologic therapies aimed to block specific cytokines in the inflammatory pathway. These children are not immunosuppressed to the degree used in other conditions such as SCID or with organ transplant where the increased incidence of plantar warts and recalcitrant warts has been reported, but anecdotally these children appear to have a greater prevalence of VP infections. Prevalence of VPs has not previously been investigated in this group of children. One study has suggested that, compared to a healthy control group (children with ADHD), children with JIA have a greater risk of opportunistic infections such as *herpes zoster* [19], it is therefore possible that this group is also at risk of developing verrucae and that these may be of a more severe nature with a longer duration. This study aims to identify the prevalence of VPs in children with JIA and other paediatric rheumatological diseases, to investigate the nature of the VPs in terms of their duration, resistance to previous treatment, demography and clinical HPV type as well as the patient's psychological reaction to the presence of VPs.

Method

Agreement for the study was provided by the hospital R&D Office. Children attending out-patient appointments within the paediatric rheumatology department on 10 separate days between Dec 2018 and Dec 2019 were approached to take part in the study. Children were identified and invited to take part in the study if diagnosed with a condition whereby the rheumatology consultant was the lead clinician, and the young people were aged between four and 17 years old. Children assenting to the study underwent a visual inspection of both feet to identify potential VPs; a dermatoscope was used for closer visualisation to confirm diagnosis when necessary. Diagnosis of a VP was confirmed on observation of the typical features such as localised hyperkeratosis, pin-point haemorrhages / capillary thrombi and disruption of dermatoglyphic pattern. Clinical typing of the HPV was determined by appearance [20]:

Deep plantar wart – single, large verruca with increased overlying hyperkeratosis (typically HPV 1 (see Fig. 1))

Endophytic wart – small, multiple warts with light hyperkeratosis often occurring in clusters (typically HPV 4)

Mosaic – plaques of verrucae (typically HPV 2)

The location/s of the VPs were recorded along with onset and duration of presence, previous treatments, presence of VPs in other family members and psychological impact. The family's own understanding of verrucae was sought along with their desire for further information on the condition.

Patient information obtained included age, diagnosis and medication taken.

Figure 1: Deep plantar wart (HPV 1).

Results

A total of 77 children were invited to take part in the study. Two children meeting the inclusion criteria declined to take part in the study and four were excluded after review of their medical records showed that their conditions did not meet the inclusion criteria (autoimmune thyroid disease, widespread musculoskeletal pain, undiagnosed condition, (non-inflammatory) pain syndrome).

The study included 71 children, ages ranged from four to 17 years old (mean = 11yrs; SD = 3.5 yrs). Seventy three percent of children had a diagnosis of Juvenile Idiopathic Arthritis. The conditions included and disease-modifying medications taken are shown in Table 1.

Table 1
Disease subtype and medication

Disease type (n)	Medication
Juvenile Idiopathic Arthritis	MTX (2); Biologic only (2); MTX + Biologic (1)
• Systemic (5)	MTX (7); MTX + Biologic (2); no meds (4)
• Oligo (13)	MTX (6); MTX + Biologic (4); no meds (1)
• Extended Oligo (11)	MTX (10); MTX + Biologic (5); Biologic only (1); no meds (1)
• Poly (17)	MTX (1); MTX + Biologic (1); no meds (2); sulfasalazine (1)
• Enthesitis Related Arthritis (5)	MTX (2); Sulfasalazine (1)
• Psoriatic (3)	No meds (1)
• Mono (1)	MTX (1); MTX + Biologics (1)
• Unclassified (2)	
Juvenile Dermatomyositis	MTX + Prednisolone (1)
JDM overlap (1)	
Vasculitides (2)	Azothiaprine (1); no meds (1)
Fever Syndromes (5)	Colchicine (2); Prednisolone (1); No meds (2)
Immunopathies (2)	Immunoglobulins (1); No meds (1)
Connective tissue disease (1)	No meds (1)
Uveitis (2)	MTX (1); MMF (1)
Other (1)	MTX + Biologic (1)

Of the group, 55 children had no VPs present, 16 children had one or more VPs. The prevalence of VPs in the whole group was 22.5%. Table 2 shows the prevalence of VPs by disease and by disease subgroup for the JIA group.

Table 2
Prevalence of VPs by disease type

Disease type	Percentage of specific group with VPs
Juvenile Idiopathic Arthritis	**22.9%**
• Systemic	• 0%
• Oligo	• 1.8%
• Extended Oligo	• 12.3%
• Poly	• 8.8%
• Enthesitis Related Arthritis	• 0%
• Psoriatic	• 0%
• Mono	• 0%
• unclassified	• 0%
Total Non-JIA Subjects	**21.4%**

Methotrexate was the most frequently prescribed medication. The chance of having a VP was greater when taking methotrexate plus a biologic rather than methotrexate alone (OR = 4.3, 95%CI 1.26 to 14.9, p = 0.026). But overall, there appeared to be no greater chance of having VPs if taking immunosuppressive medication than compared to having no medication (OR = 1.1, 95%CI 0.26 to 4.48, p = 0.46). Table 3 shows the presence / absence of VPs by medication taken.

Table 3
VP presence in relation to medication prescribed.

Medication prescribed	VP present	VP absent
None	3	11
MTX	4	26
MTX + biologic	6	9
MTX + prednisolone	0	1
Biological only	1	2
Prednisolone	1	0
Sulfasalazine	0	2
Azathioprine	1	0
MMF	0	1
Immunoglobulins	0	1
Colchicine	0	2

Only one subject associated the onset of their verrucae with the start of taking medication (Tocalizamab being added to MTX) and one subject associated their VPs with the start of a swimming programme. None of the other subjects identified a triggering factor.

Children with VPs tended to be 9 years old or older and most children had 1–3 VPs. Fewer children in the older age range (13–17 yrs) had VPs suggesting, most VPs do resolve by their teenage years. Of those teenagers with VPs, very few had recent lesions but had VPs that were several years old suggestive of these being invisible to the skin's immune system and thus being more persistent. In total, 37.5% of the young people had their VPs for 24 months or more. Table 4 demonstrates these figures.

Table 4
Subject age range and duration of VPs when present

Age range	Number without VP	Number with VPs	VP duration		No of VPs present per subject	
					1–3	+4
4–8 years	16	2	< 6m	1	2	
			6m	1		
			6-12m			
			12m			
			18m			
			24m			
			> 24m			
9–12 years	16	9	< 6m	2	7	2
			6m	1		
			6-12m	3		
			12m	1		
			18m	1		
			24m	1		
			> 24m			
13–17 years	23	5	< 6m	2	4	1
			6m	3		
			6-12m			
			12m			
			18m			
			24m			
			> 24m			

All verrucae occurred on the plantar surface with none seen on the dorsum of the digits or in the interdigital spaces. The deep plantar wart (HPV 1) was the most frequently seen VP type, being present in 12 of the 26 individually counted verrucae. When this type was identified only one or two lesions were present per foot in 75% of the cases. Endophytic VPs (HPV 4) were counted in seven VPs and one case

where there were multiple endophytic VPs present; five identifiable mosaic VPs (HPV 2) were seen with one further case having multiple plaques.

When asking whether any other family member in the household had verrucae, there were three cases (18.75%) of the children with VPs reporting someone else in the household having with verrucae, compared to three children without verrucae (7%) but this was non-significant (OR = 2.62, 95%CI 0.48 to 14.38, p = 0.13).

Less than half the subjects with a VP knew that it was a wart (n = 7), of the remaining nine subjects, three had no idea what a verruca was, three recognized it was a type of infection (virus / germ / contagious spot) and three subjects thought it was hard skin or dirt. Despite not being entirely clear on what the lesions were, the majority of subjects (81%) had sought treatment for the VPs. This consisted of over the counter (OTC) remedies in 10 cases (typically Bazuka gel which contains 12 to 26% salicylic acid), one was advised by pharmacist to watch & wait, one by a GP to "*rub it with a stone*", and one had tried laser treatment. Of the 13 subjects trying treatment, only the laser treatment was considered, by the subject, to be successful although that subject still had VPs present on observation. All but two subjects expressed a wish for further information about verrucae and their treatment to be available in the clinic.

When seeking their feelings about having a verruca, two-thirds of the subjects were not concerned about VPs being present, four said they "*did not like them*" being present, one subject said they were "*embarrassed*" by them and one subject said it "*made their feet look dirty and not looked after properly*".

Discussion

The study has identified that the prevalence of VPs in children with JIA and other paediatric rheumatological conditions is 22.5% which is very similar to the prevalence identified in the most recent large study (21%) of school children aged four to 12 years of age [1]. Unlike other conditions where the immune system is suppressed or compromised and a much higher prevalence of warts have been identified, in children with rheumatic conditions there appears to be no greater risk of developing VP infection than is seen in the healthy population. The prevalence of VPs also reduced from young children into the teenage years suggesting that in most cases the immune system can recognise and resolve these infections. However, in this group and particularly in the teenagers, 37.5% of children had VPs that were over two years old. This is only slightly more than would be expected to be seen in an otherwise healthy population where approximately 33% of cases would be expected to continue beyond two years [2]. Massing and Epstein [2] is the only study that measured prevalence beyond one year however their study included an institutionalised population such that environmental situations were very different between this and the current study.

The peak prevalence of VPs was found in the nine- to 12-year-old age group and the majority had only 1–3 VPs which also shows similarity to the typical childhood population [1, 5]. The most frequently presenting VP was the deep plantar wart which occurred as a single lesion. This has previously been linked to HPV 1 infection [20] however Bruggink *et al* [5] identified the most prevalent HPV types in single

warts (including hand warts) as being from types HPV 27 (24%), HPV 57 (22%), HPV 2 (22%) and HPV 1 (19%). Despite the variety of HPV types presenting as a single lesion, their study found that HPV 1 showed a distinct profile with it being found in children of less than 12 years old, presenting with four or fewer warts and occurring on the plantar surface and being of less than six months duration. The single VPs seen in the paediatric rheumatology subjects fits this profile of the most common lesion seen in the healthy childhood population.

In the current study there was no increased risk of having a VP when a family member was affected by VPs. In the past, VP infection was associated with swimming pools [21] and then more specifically to shower and locker room areas [22]. More recently Van Haalen *et al* [23] found that environmental factors connected to barefoot activities such as public showers or swimming pool were not related to the presence of warts but were related to family members or other members of the school class having warts. The study found an increased risk of the presence of warts when a family member had warts (OR 1.9, 95%CI 1.3–2.6) and agreement was found in a further study by Bruggink *et al* [24] which calculated a Hazard Ratio of 2.08 (95% CI 1.52–2.86) when a family member had VP infection. Both studies were much larger study than the current study and so differences between studies may be related to the small sample size of the current study. It might be argued that children with rheumatic conditions may be participating in sports and barefoot activities less that healthy children thus having less peer-barefoot contact, however it is unlikely that their condition is impacting on the amount of barefoot-contact time they are having in their own households.

Although being on medication in general did not increase the chance of having VPs in this group of children, there was an increase chance of having VPs when on biologic agents. This was seen in children taking methotrexate and a biologic therapy compared to methotrexate alone. This may be due to the small numbers involved in the study. Methotrexate inhibits DNA synthesis thus reducing the body's ability to generate an auto-immune response. It will therefore not be able to generate a full immune response to invading organisms and as such live vaccines should not be given to patients on methotrexate, and susceptibility to viral warts in a listed side effect (https://www.ouh.nhs.uk) [25]. However, by the very fact that DNA synthesis is reduced by methotrexate, the VP may move into a latent state and although not resolving or multiplying, will remain in the epidermis for longer periods than seen in a healthy population. The biologic therapies often target TNF-α which plays a critical role in the control of viral infection since it is involved in recruiting and activating macrophages, Natural Killer, T cells, and antigen presenting cells. Reduction of TNF-α by treatment with TNF-α blockade may increase the risk of developing a viral infection such as HPV [26] or not being able to resolve an infection when it occurs. One case study has reported on extensive VP infection in a 17-year-old girl receiving etanercept for treatment of JIA [27]. The VPs resolved soon after the medication was stopped.

The children in the current study showed the same psychologically concerns about having a VP infection and expressed their feelings using similar terms, such as feeling the feet were dirty or being embarrassed by the lesions. The numbers of young people reporting these concerns were similar between this and another study (33% vs 30% respectively) [1]. However, in the current study it was more typical for the

parents to seek treatment of the VPs (81%) compared to the healthy population, where only 38% had sought treatment in the Bruggink study [1], and 87.5% of those with VPs present wanted further information on VPs. This might reflect the heightened medical concerns of the parents of children with long-term conditions.

Conclusion

This is the first study to evaluate the prevalence of verrucae pedis in a paediatric rheumatological population. Children with JIA and other rheumatic conditions have no greater prevalence of VPs compared to the general population. The VPs present were of a similar clinical type and did not seem to be more widespread or unusual as has been reported in other immunocompromised populations. VPs prevalence peaked in the 9–12 years age group and had resolved by the teenage years in the majority of cases. There was a slight increased percentage of lesions remaining beyond 24 months than has been reported in other healthy populations. The children in this study seemed to be less concerned psychologically about their VPs, despite this most families had sought treatment for the verrucae and reported that they would value further information about the condition.

Declarations

Ethical approval and consent to participate in the study was given by the Research and Development Office, Great Ormond Street Hospital, London registration no. 2399.

Consent for publication- not applicable

Availability of data and materials used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests - "The authors declare that they have no competing interests"

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Authors' contributions – the concept, data collection, analysis and manuscript were completed by the author.

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Figures

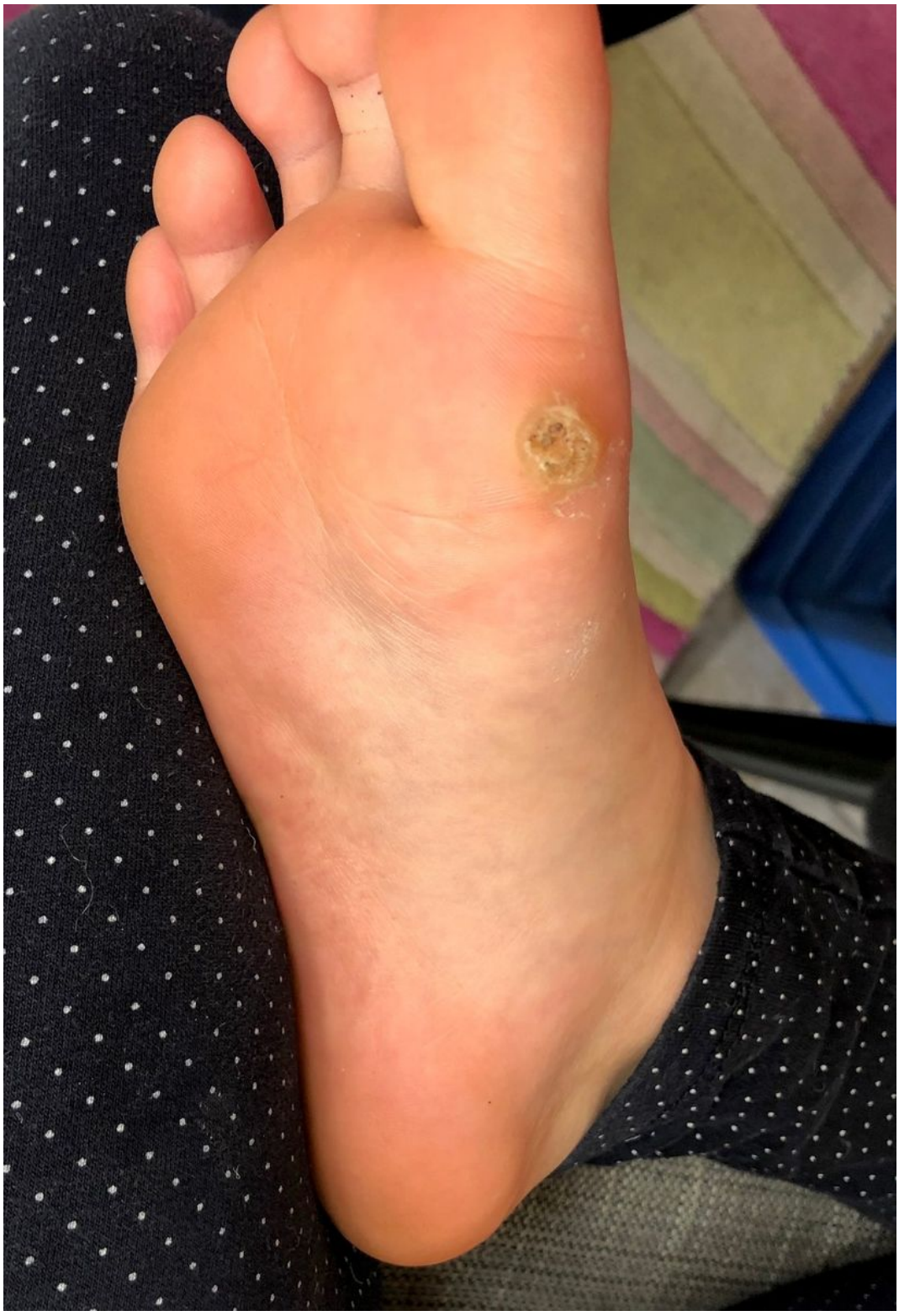

Figure 1

Deep plantar wart (HPV 1).