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Review

Male genital vitiligo

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ABSTRACT

Vitiligo is a polygenetic multifactorial disease leading to melanocytic loss in skin and sometimes in hair. Genital areas may be involved and represent a specific therapeutic challenge. Surprisingly, data on male genital vitiligo remain scarce. This review aims to collate current knowledge on male genital vitiligo and to discuss the risks and benefits of the various therapeutic approaches. Male genital vitiligo is relatively frequent and often induces marked impairment of quality of life, with a specific impact on sex life. Prompt recognition of activity remains mandatory to halt disease progression, as repigmentation remains difficult to achieve in most cases. Thanks to progress in understanding of the pathophysiology of vitiligo, new therapeutic approaches are under development. Topical ruxolitinib, a JAK pathway inhibitor, is currently the product in the most advanced stage of development, with a very encouraging repigmentation rate on the face, although specific efficacy in genital area remains to be assessed. The next generation of treatments, such as topical WNT agonists, could be of great interest in genital vitiligo as they will not require combination with UV therapy and they may be able to enhance the differentiation and proliferation of melanocyte stem cells in this difficult-to-treat area.

1. Introduction

Vitiligo is a polygenetic multifactorial disease leading to melanocytic loss in skin and sometimes in hair. Genital areas may be involved and represent a specific therapeutic challenge. Genital vitiligo can markedly impact the sex life of patients. Surprisingly, data on male genital vitiligo remain scarce. This review aims to collate current knowledge on male genital vitiligo and to discuss the risks and benefits of the various therapeutic approaches.

2. Epidemiology

There are limited data on the incidence of genital vitiligo in the general population. In a population of 1000 men attending a sexually transmitted diseases (STD) center in the United Kingdom, genital vitiligo was observed in only 3 patients [1]. In another series of 5000 male dermatology consultants, hypochromic or achromic genital macules were observed in 38 cases, 22 of which involved vitiligo (0.44%) while 16 involved post-inflammatory depigmentation [2]. The genital location of vitiligo may either be isolated or it may be the first location for many years. Most frequently, it is associated with extra-genital lesions. In a French population of 509 patients with vitiligo, genital involvement was present in 32% of patients, with no difference according to phototype [3]. The same results were reported in a cohort of 700 vitiligo patients in Belgium, where genital involvement was observed in 34.5% of patients [4]. Interestingly, the genital area was more frequently affected in males (45.5%) than in females (24.6%) ($P < 0.001$). Thus, based on the prevalence of vitiligo (0.5 to 2% of worldwide population), genital vitiligo is expected to be observed in 0.15 to 0.66% of the population.

3. Clinical presentation

Since vitiligo is asymptomatic, the usual reason for consultation is aesthetic distress rather than possible pruritus during the initial inflammatory phase. Male genital vitiligo presents as well-defined, hypochromic macules on hair-bearing cutaneous areas (scrotum, penile shaft, pubis) and/or on hairless, semi-mucous genital areas (glans and inner foreskin) (Fig. 1). The achromic macule may have a hyperpigmented border, resulting in trichrome vitiligo, which is more easily seen on darker skin (Fig. 2). Leukotrichia is frequent (Fig. 3) and involvement of the perineum and/or the gluteal folds can occur (Fig. 4). Signs indicating activity of vitiligo should be sought at each consultation. These include

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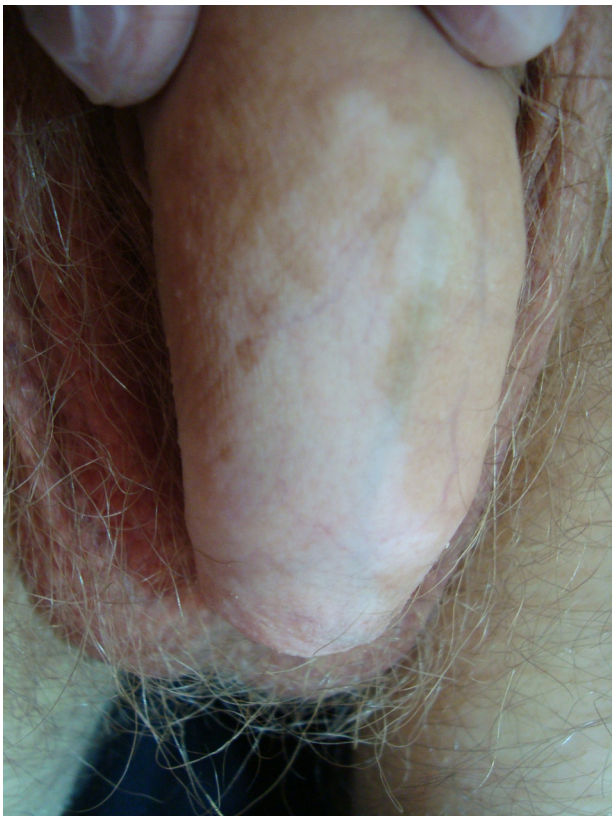

Fig. 1. Vitiligo of the shaft of the penis.

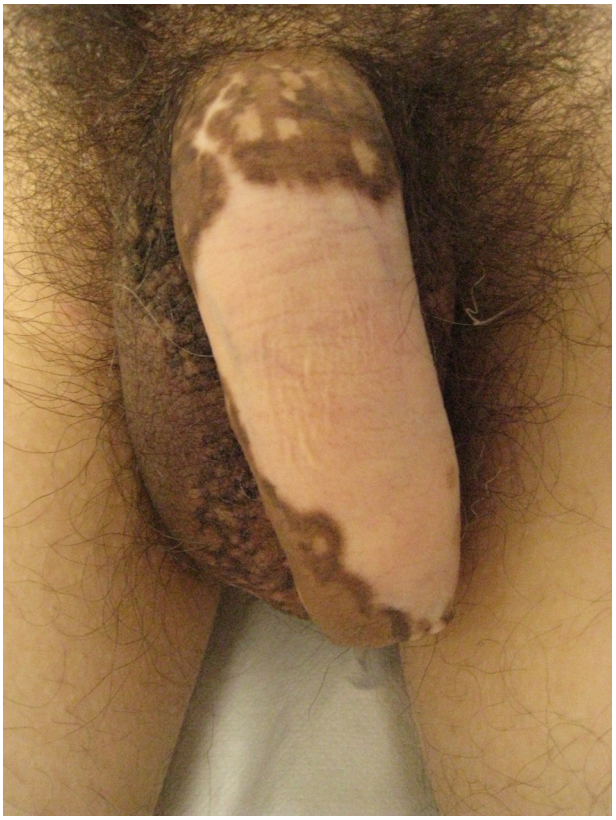

Fig. 2. Trichrome vitiligo.

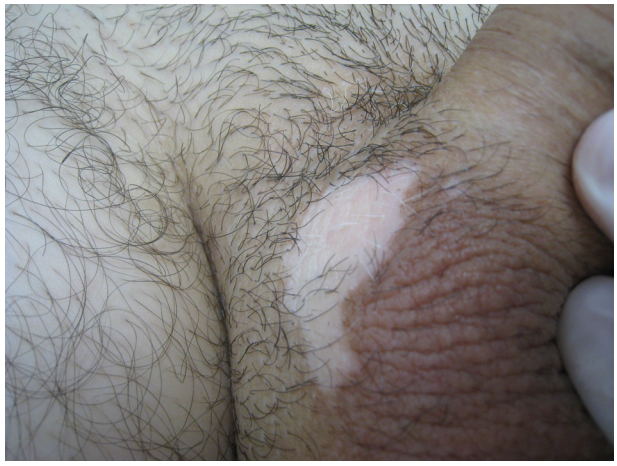

Fig. 3. Vitiligo with leukotrichia.

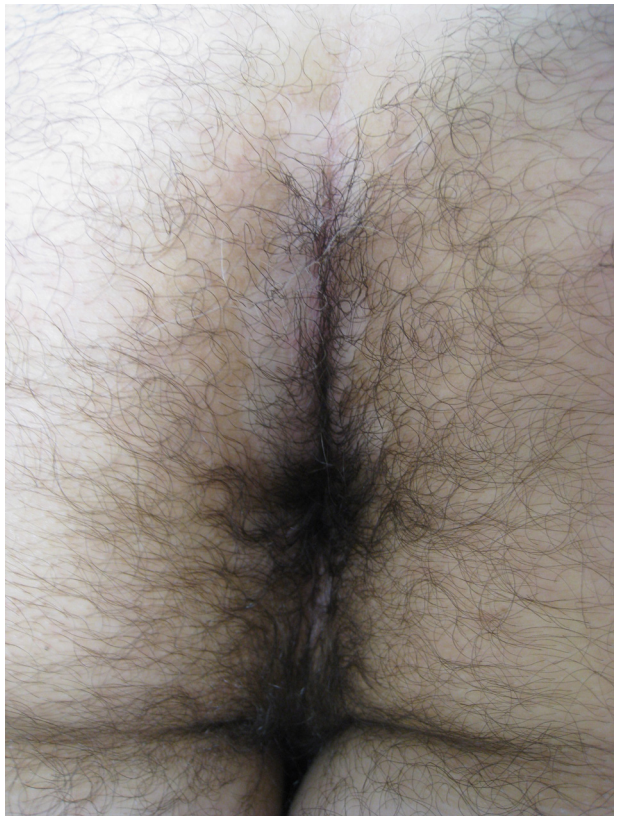

Fig. 4. Vitiligo of the intergluteal cleft.

inflammatory borders (although rare), hypochromia at the edge of achromic lesions, poorly defined borders, confetti lesions and Koebner's phenomenon [5]. Genital lesions can be triggered or aggravated by Koebner's phenomenon caused by tight-fitting underwear [6,7].

Clinicians must be aware of vitiligo-like depigmentation that may appear in hyperpigmented lesions of genital melanosis. The association of depigmentation and hyperpigmented melanosis may be mistaken for melanoma. However, the clinical presentation is very different, with large homogeneous hyperpigmentation macules, followed after several months or years of progression by depigmented lesions (Fig. 5) [8,9]. It is still debated whether this presentation should be considered as vitiligo rather than autoimmune melanocyte destruction on genital melanosis. A similar

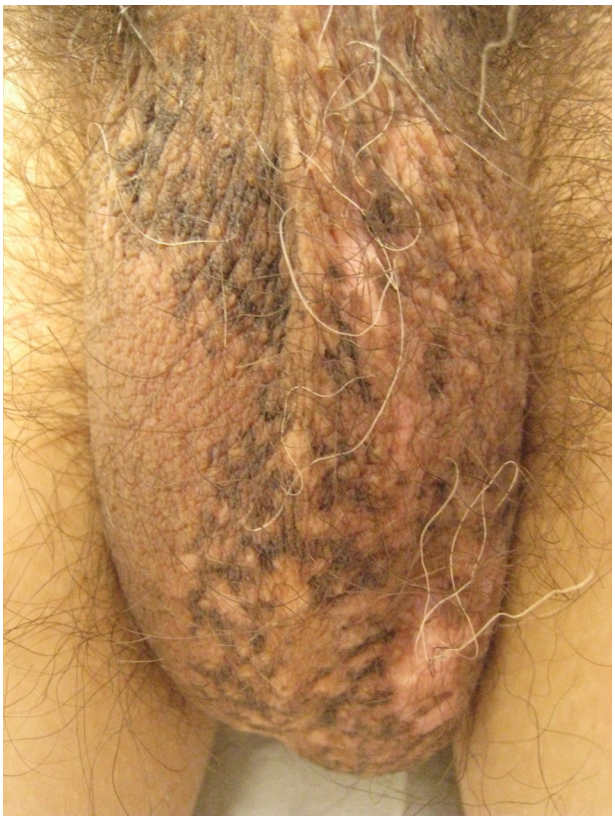

Fig. 5. Vitiligo with reticular hyperpigmentation.

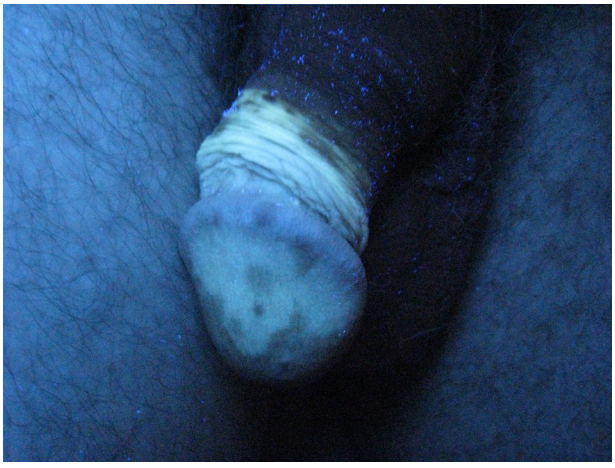

Fig. 6. Vitiligo of the penis seen with Wood's lamp.

presentation may be observed in nipple melanosis. The absence of development of vitiligo lesions in other parts of the body despite years or decades of progression argues in favor of a specific autoimmune reaction as observed in halo-nevus [9]. Examination of the genital area with Wood's lamp is essential, especially in fair skin, to better delineate the lesions and detect both signs of activity or repigmentation (Fig. 6) [10,11].

Several severity scores for vitiligo have been developed and validated. The VASI (Vitiligo Area Severity Index) is not useful in genital vitiligo since the genital area is not included in calculation of the score [12]. The VES (Vitiligo Extent Score) could be of greater use for genital vitiligo since it takes into account the extension of vitiligo in 19 areas, including the genital and peri-genital area [13]. There is no severity score dedicated to genital vitiligo.

Table 1
Differential diagnoses of male genital vitiligo.

Specific genital dermatoses	General dermatoses with genital localization
Vitiligoid lichen sclerosus	Achromic pityriasis versicolor
Corticosteroid-induced depigmentation in lichen sclerosus	Post-inflammatory depigmentation of genital psoriasis
Hypopigmented allergic contact dermatitis to condom latex	Genital atopic dermatitis
Hypopigmented extramammary Paget's disease	Hypopigmented mycosis fungoides
Hypopigmented Bowen's disease	Tuberculoid leprosy
Syphilis	
Genital hypopigmentation following cryotherapy or laser vaporization of condylomas	
Genital hypopigmentation secondary to the application of imiquimod	
Vitiligoid-depigmentation in melanoma	

Genital involvement can be present in all types of vitiligo: non-segmental, segmental and mixed, depending on the distribution of extra-genital lesions. When the genital lesion is isolated and limited in size, vitiligo is said to be unclassifiable (based on current classifications), pending a definite classification that relies on the extension of the lesions or the appearance of new extragenital lesions [14].

4. Impact on quality of life

An assessment of the impact on the patient's general quality of life must be made as genital vitiligo seems to have a greater impact than non-genital vitiligo, even if some studies have not been able to show any difference [15,16]. A non-vitiligo-specific score such as the Daily Life Quality Index (DLQI) may be used, or vitiligo-specific tools such as the VitiQoL or the VIPs (Vitiligo Impact Patient scale), but they do not include a specific item of genital involvement [17,18]. Of note, genital involvement is also a risk factor for depression in vitiligo patients, with no difference being observed between men and women in most studies [19].

Finally, impact on the quality of sexual function should be assessed, since it has been shown that vitiligo with genital involvement may be a risk factor for sexual dysfunction [20,21]. While the VitiQol score does not take into account the sexual impact of vitiligo, this may be evaluated using Question 9 of the DLQI ("Over the last week, how much has your skin caused any sexual difficulties?"), or by the two items on the VIP score (Vitiligo Impact Scale) ("My vitiligo has a negative impact on my libido" and "My vitiligo is an obstacle to my sexuality") [18].

5. Pathology

The diagnosis of genital vitiligo is clinical and does not usually require laboratory investigations. In some cases involving an unusual clinical presentation or diagnostic doubt, skin biopsy may be performed. Histology shows a decrease or absence of intra-epidermal and/or intra-epithelial melanocytes. The detection of melanocytes can be enhanced by immunohistochemistry markers: PS100, Melan-A, HMB45 or SOX-10. In cases of inflammatory vitiligo, a dermo-epidermal mononuclear infiltrate is present and must not be confused with epidermotropic lymphoma.

6. Differential diagnoses

Only the differential diagnosis of isolated genital vitiligo is discussed herein (Table 1). Full body skin examination,

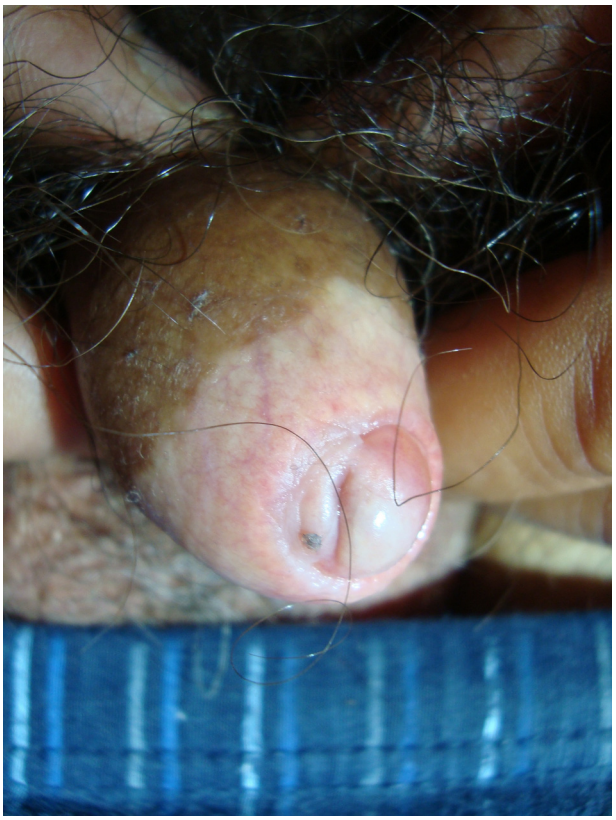

Fig. 7. Vitiligoid lichen sclerosus.

history-taking and biopsy results will rule out other acquired genital hypomelanoses. Differential diagnoses include genital involvement of achromic pityriasis versicolor, pityriasis alba, post-inflammatory depigmentation of genital psoriasis (with possible lesions suggestive of psoriasis on the periphery or in the center of hypochromic plaques forming a hypochromic Woronoff ring), genital atopic dermatitis, hypopigmented mycosis fungoides, or tuberculoid leprosy (hypoesthetic hypochromic lesions) [22,23].

Other differential diagnoses, more specific to the genital area, include:

- vitiligoid lichen sclerosus, which is a clinical form of lichen sclerosus of the glans and foreskin, where hypochromic foreskin fibrosis or phimosis is associated with histological findings of lichen sclerosus (Fig. 7) [24]. This could be an atypical form of lichen sclerosus or a vitiligo/lichen sclerosus overlap. It must be distinguished from coexistence of both diseases, for example lichen sclerosus of the glans and foreskin associated with vitiligo of the penile shaft [25];
- corticosteroid-induced depigmentation in lichen sclerosus and other dermatoses, usually associated with skin atrophy (Fig. 8);
- hypopigmented allergic contact dermatitis to condom latex [26];
- hypopigmented extramammary Paget's disease [27];
- syphilis: leukoderma (post-secondary syphilis), gumma, post-gummatous atrophic scar [28];
- hypopigmented Bowen's disease (HPV-induced intraepithelial neoplasia) (Fig. 9);
- genital hypopigmentation secondary to the application of imiquimod for the treatment of condylomas. In this case, the physiopathology is questionable: induced vitiligo or simple post-inflammatory depigmentation [29–31];
- genital hypopigmentation following cryotherapy or laser vaporization of condylomas (Fig. 10);

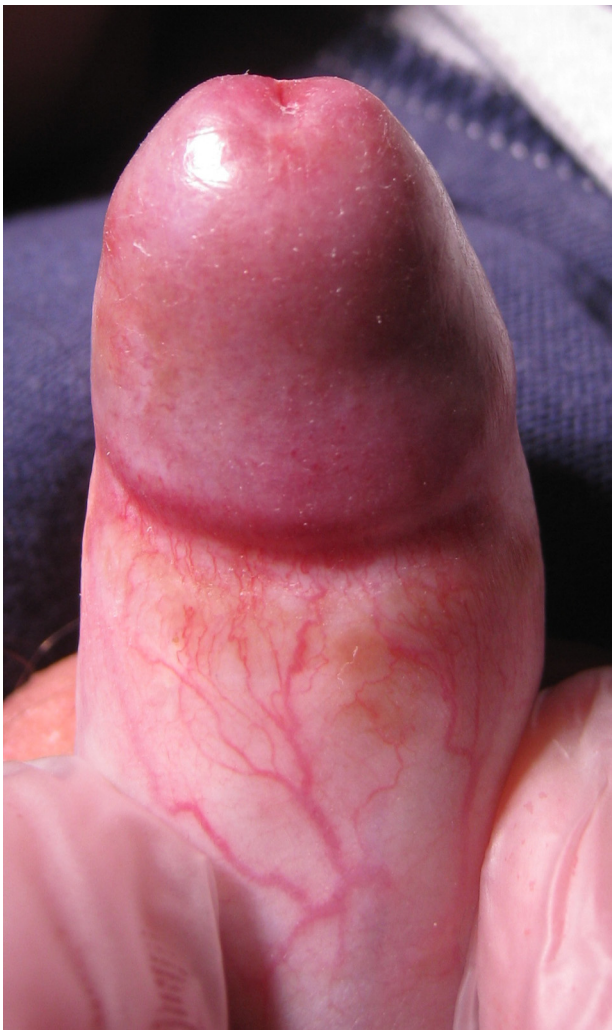

Fig. 8. Hypochromia of the foreskin secondary to the application of topical corticosteroids for lichen sclerosus in a child.

- vitiligo-like depigmentation in melanoma may occur in the case of depigmentation in genital melanosis. The hyperpigmentation is homogeneous with well-defined borders in genital melanosis, and the hyperpigmentation usually spreads throughout a relatively large area compared to melanoma. A biopsy for histological analysis is mandatory if there is any clinical doubt.

7. Autoimmune assessment

Since vitiligo is an autoimmune disease that may be associated with autoimmune thyroiditis, especially in the case of non-segmental or late-onset vitiligo, laboratory investigations including TSH, anti-thyroperoxidase and anti-thyroglobulin antibodies should be performed routinely, even in the absence of clinical signs [14,32]. It is usually recommended to search for autoimmune thyroiditis every 3 or 4 years.

8. Treatment

Therapy begins with educating the patient about the chronic nature of genital vitiligo and the objectives of treatment: to prevent the extension of lesions by blocking the immune response against melanocytes and to induce melanocyte differentiation and proliferation to promote repigmentation. Finally, when repigmentation is achieved, a maintenance treatment can be proposed for

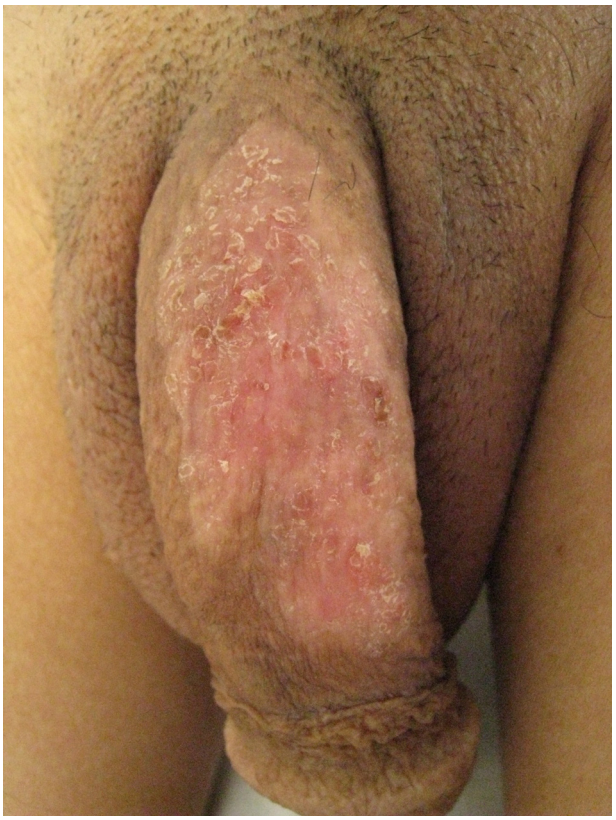

Fig. 9. Hypochromic Bowen disease.

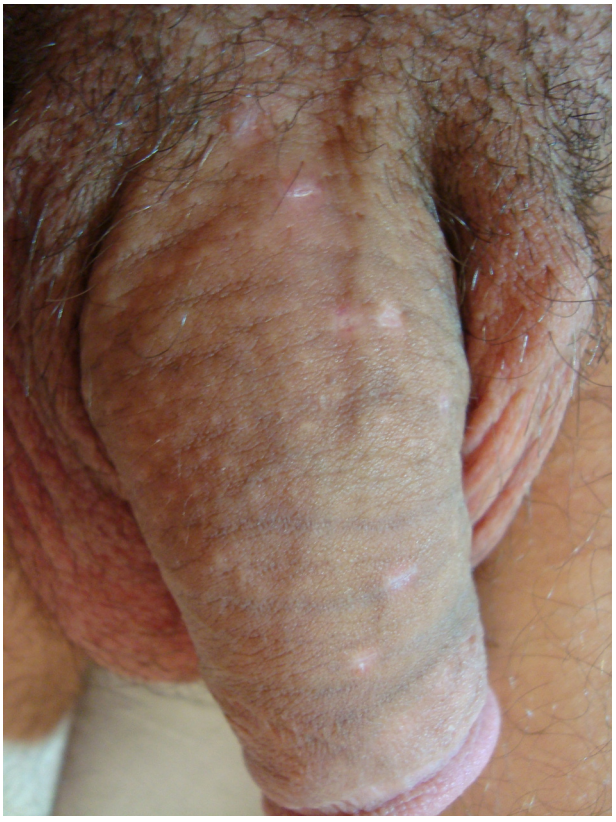

Fig. 10. Achromia secondary to vaporization of condylomas with a CO2 laser.

preventing relapses [14]. However, genital vitiligo is a difficult-to-treat localization with poor response to treatment. The patient must be informed about the possible extension of vitiligo by Koebner's phenomenon, emphasizing that there is probably a lower risk in genital forms of vitiligo than in other localizations. Importantly, Koebner's phenomenon is seen mostly in the active phase of the disease. Thus, patients should try to avoid unnecessary friction, particularly where clinical signs of activity are observed, even if this recommendation may be difficult to propose in this specific area.

Therapeutic abstention may be agreed with the patient, if lesions are old, stable, and without impact on quality of life or sexual function. There are currently no clinical trials that have specifically addressed the treatment of genital vitiligo [33].

In all cases, signs of activity must be sought. If activity is detected, treatment must be started as a matter of emergency. Systemic corticosteroids prescribed in oral minipulses (OMP), with sequential weekend treatment comprising dexamethasone or betamethasone, have been shown to halt disease progression in 91.8% of cases [34]. Although these studies did not specifically assess the efficacy of steroid OMP on genital vitiligo, personal experience supports the efficacy of this therapeutic approach in active genital lesions of vitiligo. Screening for clinical activity and prompt introduction of OMP treatment is of particular interest in genital vitiligo due to the significant impact of the condition on quality of life and the challenge of re-pigmenting this area.

In non-active forms, topical corticosteroids are indicated as first-line therapy, with daily application of a potent topical corticosteroid. For the rest of the body, an intermittent regimen should be proposed (3 weeks per months or 5 days a week for example). Early treatment improves the chances of response, although repigmentation is significantly more difficult to achieve in genital skin compared to the face. The treatment is usually well-tolerated, but human papillomavirus (HPV) reactivation is a risk in patients with a previous medical history of symptomatic HPV lesions. Twice-daily applications of topical calcineurin inhibitors, such as tacrolimus 0.1% ointment or pimecrolimus 1% cream, may be prescribed off-label as a first-line or rather as a second-line treatment [35]. As for topical corticosteroids, their efficacy has not been specifically assessed in genital vitiligo. However, topical calcineurin inhibitors might be less effective in vitiligo affecting photo-protected areas as in genital vitiligo than in facial vitiligo [36]. They do not present a risk of skin atrophy with prolonged use but have a similar risk of HPV reactivation. Topical steroids or topical calcineurin inhibitors should be prescribed for 6 months. Patients then need to be re-evaluated using Wood's lamp. Treatment should be continued only if repigmentation signs are observed. In all cases, patients must be informed that vitiligo lesions usually require 6 to 24 months of treatment to achieve a complete or almost complete repigmentation.

Phototherapy is usually contraindicated for the treatment of genital vitiligo, due to the increased risk of genital squamous cell carcinoma that has been reported after phototherapy for psoriasis [37]. It is therefore important to shield the genital area when treating extra-genital vitiligo with phototherapy. However, some authors consider the genital area as a relative contraindication and expose only the scrotum and penile shaft to phototherapy and cover the glans. Unfortunately, phototherapy results in the genital area are usually disappointing [38,39]. Importantly, although most skin cancers reported after phototherapy for psoriasis were associated with the use of UVA phototherapy, some cases have been reported after UVB treatment, not only on the penis but also on the scrotum [40]. Phototherapy should thus be carefully discussed with the patient in case of severe distress, with clear explanations of the limitations and the risks. If phototherapy is started, it must be combined with topical treatment to achieveoptimal repigmentation, with reassessment after 6 months [41].

Surgical approaches to genital vitiligo include tissue grafts and melanocyte (or epidermal) cell transplants. Surgery is indicated for localized and stable vitiligo or for segmental vitiligo that is resistant to medical treatment [42–44]. The use of camouflage techniques (self-tanning or tinted covering cream) is also possible. Dermopigmentation and cosmetic tattoos are not recommended.

When repigmentation is achieved, the risk of relapse during the first year ranges from 40 to 50%. Twice-weekly application of tacrolimus 0.1% ointment was shown to be effective in reducing the risk of relapse (9% in the tacrolimus group versus 40% in the placebo group) [45]. However, none of the patients included in this study were treated for genital vitiligo lesions.

9. Conclusions

Male genital vitiligo is relatively frequent and often induces marked impairment in quality of life, with specific impact on sex life. Prompt recognition of activity remains mandatory to halt disease extension, since repigmentation remains difficult to achieve in most cases. Thanks to progresses in our understanding of the pathophysiology of vitiligo, new therapeutic approaches are under development. Topical ruxolitinib, an inhibitor of the JAK pathway, is the most advanced in terms of development and has shown very encouraging repigmentation rates in a multicenter prospective randomized phase 2 study [46]. However, significantly better results are obtained on the face, and specific efficacy in the genital area remains to be assessed. Further data are needed but JAK inhibitors (either topical or systemic) do not seem to allow potent repigmentation in difficult-to-treat areas such as the hands or feet, but also the genitals. Next-generation treatments, such as topical Wnt/β-catenin signaling pathway agonists, could be of great interest as they will not require combination with UV treatment and might be able to enhance the differentiation and proliferation of melanocyte stem cells in these difficult-to-treat areas [47,48].

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Disclosure of interest

The authors declare that they have no competing interest.

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