Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: October 31, 2022

Citation: Garg S, Tuknayat A, et al., 2022. Is Covid Vaccine (Covishield) Giving Rise to De Novo Cutaneous Autoimmune Disorders and Aggravating the Existing Ones: A Case Series of 10 Patients with Review of Literature, Medical Research Archives, [online] 10(10). https://doi.org/10.18103/mra.v10i10.3233

DOI
https://doi.org/10.18103/mra.v10i10.3233

ISSN: 2375-1924

REVIEW ARTICLE

Is Covid Vaccine (Covishield) Giving Rise to De Novo Cutaneous Autoimmune Disorders and Aggravating the Existing Ones: A Case Series of 10 Patients with Review of Literature

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ABSTRACT

Introduction: Covid-19 which is an ongoing pandemic, has already caused millions of deaths and disabilities till date. Covid scenario and mass vaccination has completely changed the understanding of dermatological disorders. The clinicians are noticing a sudden increase in new onset autoimmune disorders and aggravation of existing ones. The study is based on 3 hypotheses i.e. antibody dependent enhancement of virus, molecular mimicry and antigen-antibody complex formation, explaining the pathogenesis involved in vaccine induced cutaneous autoimmune disorders.

Methods: In this prospective observational study, we observed 2 groups of patients following Covishield vaccine-

Group 1: appearance of new lesions pertaining to autoimmune disorders

Group 2: exacerbation of cutaneous lesions of already existing autoimmune disorder

The diagnosis was made based on appearance of clinical signs within 6 weeks of vaccination dose and the clinical diagnosis was established by at least two Dermatologists.

Results: Ten patients were enrolled in this study over a period of 6 months. Six patients (Group 1) presented with new onset of lesions whereas 4 patients (group 2) presented with exacerbation of existing autoimmune disease. Patients were given medical treatment as per disease severity along with proper nutritional support and antioxidants.

Conclusion: This article highlights the importance of creating awareness and staying vigilant for the appearance of any new autoimmune disease and exacerbation of existing disorder and for future course of action for choice of vaccination and booster doses. A chronological association in last 6 weeks of vaccination dosage must be evaluated in detail and causative association should be considered in autoimmune disorders. Whether the relationship between Covid vaccination and autoimmune phenomenon is causal or coincidental still remains unknown and large multi-centre studies are required to assess the same.

Introduction

Covid-19 caused by SARS CoV-2 virus is an ongoing pandemic which has caused millions of deaths till now. Initially thought to be a respiratory virus, it is now a proven fact that it can involve almost all the systems of the body. The main underlying pathogenic factors being cytokine storm and micro-thrombosis involving multiple organs, including skin causing excessive immune activation.[1] Cutaneous manifestation of Covid are now well known which include, maculopapular rash, urticaria, Covid toes, livedo like lesions to name a few.[2]

Many vaccines have come up to stop the spread of this rapidly progressing virus like DNA vaccines, mRNA vaccines, replicating and non-replicating vector vaccines. Most of these vaccines have been approved without extensive studies on their side-effects and efficacy. In India, Covishield (Astra Zeneca covid-19 vaccine) and covaxin are the two main vaccines that are being administered. Covishield is a non-replicating viral vector vaccine.[3,4] Based on the phase 3 trials, this vaccine has an efficacy of 72 % against symptomatic SARS-CoV2 virus. These vaccines have a few proven side effects like allergic reactions, anaphylaxis, pain at injection site, fever and thrombotic events (thrombosis with thrombocytopenia syndrome).[5]

Autoimmunity is a loss of self-tolerance mechanism of the body and it is usually a result of a multitude of factors. Once diagnosed or manifested, they usually require lifelong therapy. The role of viral infections like cytomegalovirus, hepatitis A, coronaviruses, etc in triggering or causing autoimmune diseases has been studied in detail in literature. The possible mechanisms implicated include molecular mimicry, bystander inflammation, epitope spreading or exposure of cryptic antigens. It is a well-known fact that autoimmune disorders are being triggered or exacerbated by Covid-19 virus[6] but interestingly in some patients these disorders are being triggered by the vaccine itself. Many cutaneous side effects of these vaccines like Type IV hypersensitivity reaction, Lichen planus, Covid arm (delayed inflammatory reaction), Cutaneous vasculitis, autoimmune subepidermal bullous disease have been reported.[7,8,9,10] Role of adjuvants used in vaccines in causing autoimmunity has also been studied and cannot be ignored.

This case series is an attempt to discuss the skin manifestations after Covid vaccination and the underlying pathogenesis by extrapolating the data already known to us. It also discusses the scenarios where a physician needs to be cautious while administering these vaccines. We also want to reiterate the fact that vaccine induced autoimmune disorders are very rare and it should not undermine the benefits of vaccination.

This is a case series wherein we observed that there were 2 groups of patients, one where there were appearance of new lesions pertaining to autoimmune disorders like vitiligo, lichen planus, Discoid lupus erythematosus (DLE) and the second group where there was exacerbation of cutaneous lesions of already existing autoimmune disorder. Interestingly, all the patients in the present series had received the same vaccine i.e. Covishield which is a mRNA recombinant vaccine.[3,4]

Though few case reports of Covid vaccine induced autoimmune phenomenon have been reported in the last 1 year, this is the first Indian case series to do the same.

Case series

The details of the patients have been summarized in the following table which includes the morphology and distribution of lesions, clinical diagnosis, number of vaccine doses taken, duration post vaccination when the lesion appeared and the treatment given to the patient.

New Onset Autoimmune Diseases

S.No	Morhology	Distribution	Diagnosis	Duration Post Vaccination	Sars Cov-2 Igg Ab Level (Spike Protein)U/Ml	No. of Doses Taken	Treatment
1	Multiple well defied gradually progressive depigmented macules	Left angle of the mouth, which later progressed to the left side of the nose and left eyebrows involving the hair	Segmental vitiligo with leukotrichia	15 days post 1st vaccine	>20	2	Medium potency steroid Tacrolimus Antioxidant Protein supplement
2	Multiple ill to well defined itchy reddish firm papules and plaques. Maculopapular malar rash over the face. Some lesions were DLE like with central clearing, follicular plugging and atrophy. (Figure A)	Dorsum of the hands and forearms, neck, forehead and face	LP –DLE overlap	20 days post 1st vaccination flare up after 2nd dose	>20	2	Sunscreen Medium potency steroid Tacrolimus Antioxidant Protein supplement Antihistamine Hydroxychloroquine
3	Multiple ill to well defined itchy maculopapular eruptions. These lesions were of reticulate pattern. (Figure B)	Extensors of forearm, back and thighs.	Reticulate maculopapular rash	6 weeks post 1st vaccination	>20	2	Antihistamine Medium potency steroid Tacrolimus Protein supplement
4	Asymptomatic single well defined oval depigmented macule with leukotrichia. (Figure C)	Left underarm	Vitiligo with leukotrichia	15 days post 1st vaccination	>20	2	Medium potency steroid Tacrolimus Antioxidant Protein supplement UVB
5	Multiple round to oval hyperpigmented, violaceous plaques (Figure D)	Both legs and inner thighs	Lichen planus	1 month post 2nd vaccination	Not done	2	Medium potency steroid Tacrolimus Antioxidant Protein supplement Antihistamine
6	Single well-defined patch with loss of hair (Figure E)	Occipital area	Alopecia areata	1 month after 1st dose	>20	2	Minoxidil+tretinoin+azelaic acid combination Hair supplements Protein supplement

Abbreviations- S No- Serial number, NO. – Number, SARS- Severe acute respiratory syndrome, LP-Lichen planus

Exacerbation of existing diseases

S.No	Morhology	Distribution	Diagnosis	Duration Post Vaccination	Covod Antibody Levels	No.Of Doses Taken	Treatment
1	Multiple depigmented macules	Trunk	K/c/o vitiligo	3 weeks after the 2nd dose	>20	2	Oral methotrexate15mg/week Medium potency topical steroid Tacrolimus Antioxidant and supplements Protein supplement
2	Well-defined patch of hair loss	Right eyebrow	K/c/o aa with nummular eczema	2 weeks after 1 dose	>20	2	Minoxidil+ tretinoin+ azelaic acid combination Hair supplements Antioxidant Protein supplement
3	Multiple grayish-violaceous velvety papules and plaques with annular and retiform pattern (Figure F)	Bilateral buccal mucosa	K/c/o cutaneous lichen planus with new lesions of oral lichen planus	1 week after 2nd dose	>20	2	Oral and topical medium potency steroid applications Pure oral glycerin Oral and topical tacrolimus Oral multivitamin supplements Protein Supplements
4	Rapidly progressing Multiple depigmented macules (Figure G)	Trunk and extremities	K/c/o vitiligo	4 weeks after the 2nd dose	>20	2	Oral methotrexate15mg/week Weekend oral mini pulse therapy Medium potency topical steroid Tacrolimus Antioxidants and supplements Protein supplement

Abbreviation – K/c/o – Known case of

The diagnosis of all the patients is based on their clinical examination by at least two dermatologists. Skin biopsy was done for one of our patients who was resistant to the conventional treatment and the histopathological report was consistent with lichen planus (hydropic degeneration of basal layer, subepithelial lymphocytic infiltrate and there was band like lympho-histocytic infiltrate at the dermo-epidermal junction. Also, there was keratotic plugged follicle with inflammation of the superficial epidermis which consists of lymphomonocytes.)
On dermoscopy for the same patient we found prominent follicular plugging, atrophy which was consistent with LP overlap discoid lupus erythematosus (Figure H)

Discussion

Covishield vaccine is a single recombinant, replication deficient chimpanzee adenovirus vector encoding SARS-COV2 spike glycoprotein produced in genetically modified human embryo kidney (HEK) 293 cells.[3,4]
When this vaccine is injected into the human body, it triggers the immune reaction by activation of T cells. There is increase in CD8 T cell count which further leads to B cell activation and formation of neutralizing antibodies against the virus. Antibody formation takes place at around 2-3 weeks and these are of IgG type which stay for an extended period of time.[11]
It is a well-known fact that autoimmune disorders are being triggered or exacerbated by Covid-19 virus but interestingly in some patients these

disorders are being triggered by the vaccine itself. Autoimmune phenomenon is well postulated in viral diseases via mechanism known as epitope spreading.[12,13]

In our cases there was triggering of autoimmunity due to vaccination which lead to cutaneous manifestations like vitiligo, DLE like lesions, maculopapular rash, etc, which is relatively a newer concept.

So, we have following hypotheses which explains the triggering mechanism for autoimmune diseases in response to vaccination as a foreign antigen. (Figure I)

SARS-CoV2 has a spike glycoprotein which binds to the ACE (angiotensin converting enzyme) receptor in the cells. This receptor is being shared by many cells including cells of the spleen, lung, skin and endothelium. The vaccine contains a part of the spike glycoprotein which in some predisposed individuals can bind to the same ACE receptor and trigger a hyperimmune reaction and cytokine storm which can mimic Covid-19 infection and thus cause autoimmunity. These predisposing factors include genetic predisposition, physical factors, hormonal factors, infections and nutritional deficiencies (deregulated autophagy)[14]. This leads to activation of T cell leading to antigen-antibody reaction, release of type 1 interferons and formation of other complement complexes which bind to the triggering auto immunity. Thus, the adaptive immune response which a vaccine displays for its protective effect, could simulate a hyperinflammatory condition.

Second hypothesis could be because the vaccine is new, it might contain certain foreign antigens which cross react with human tissues (molecular mimicry) leading to auto-immunity.[13,15,16]It is already known that SARS-CoV2 spike glycoprotein and lung surfactant share 13 of 24 pentapeptides, which leads to cross reactions between immune response after Covid-19 infection, causing the predominant deadly respiratory manifestations of Covid-19, leading to acute respiratory distress syndrome. There could be cross reaction between SARS-CoV2 proteins and other tissue antigens as they may have shared epitopes which may lead to auto-immunity against skin and connective tissue. In addition, being a chimpanzee adenovirus it might react with certain human antibodies and trigger auto immune reaction. It is important to note that only a minority of the vaccinated population develop autoimmunity, indicating that other factors like genetic predisposition play an important role.

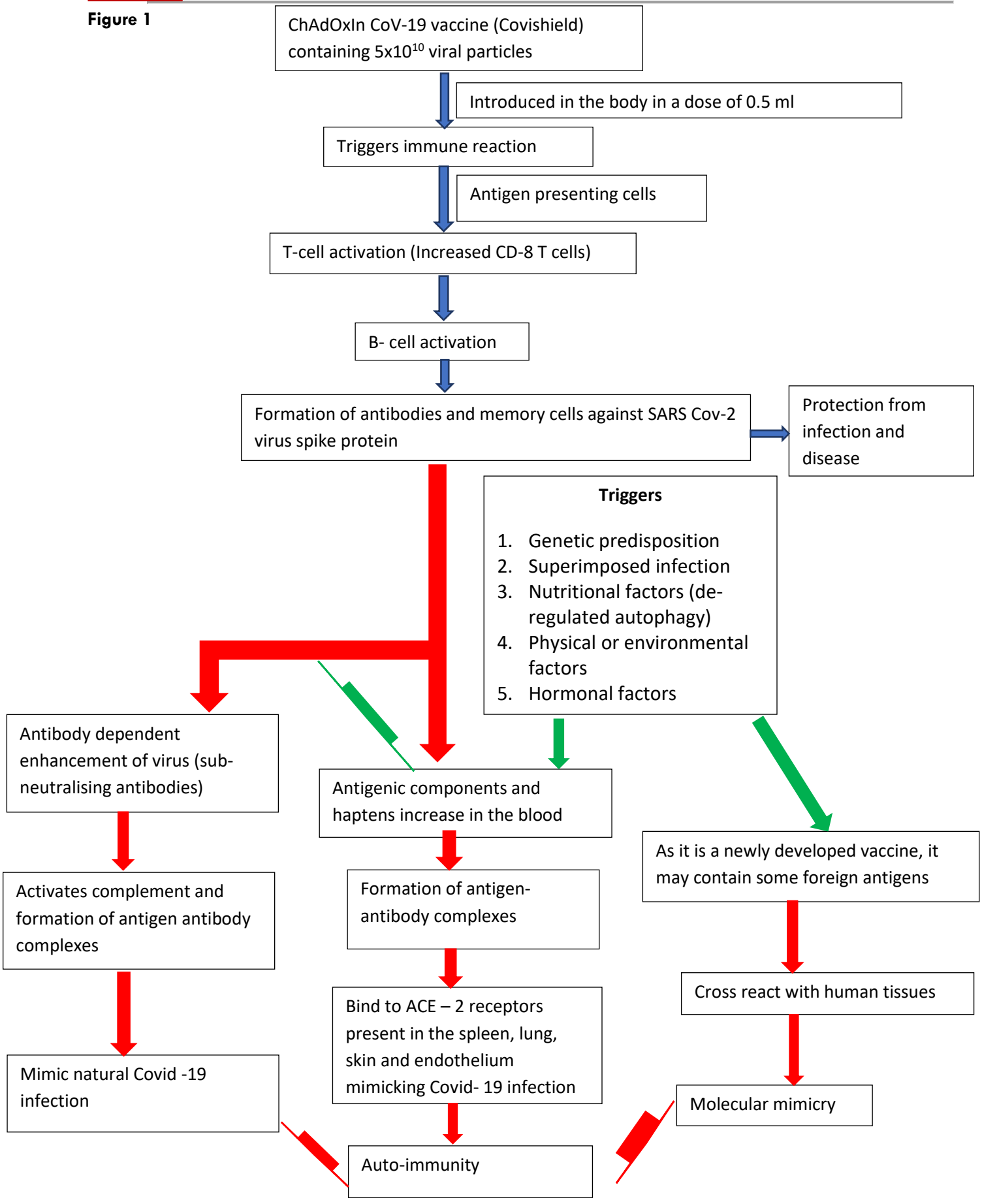
In addition, vaccine adjuvants can also play an important role in rendering a vaccine immunogenic. Adjuvants like pegylated ethylene glycol, histidine and non-ionic surfactant like polysorbate-80 could trigger the NLR pyrin domain containing 3 (NLRP3) inflammasome which is identified by toll like receptors and thus can activate inflammation and immunity causing realease of interleukin 1b, interleukin-6, macrophage inflammatory protein b. NLRP3 plays a major role in many autoimmune diseases like systemic lupus erythematosus, Sjogren syndrome, inflammatory bowel disease and systemic sclerosis.

Antibody enhanced viral replication which is a sub neutralizing antibody response which further activates complement and formation of antigen antibody complexes (like in Ebola, dengue) which mimics natural covid-19 infection may also be implicated in causing autoimmunity.[12,13]

In our case studies the target cells have been epidermal melanocytes in case of vitiligo and melanogenesis related peptides in alopecia areata with majority of immune infiltration occurring deeper in the skin, in and around the hair follicle bulb.[17] There is epidermal basal cell damage and band like lymphocytic infiltration in the upper dermis in case of DLE lesions. It involves activation of keratinocytes, endothelial cells and skin dendritic cells along with production of type1 interferon followed by recruitment and activation of CD4+ and CD8+ cytotoxic T cells. There is cytotoxic keratinocyte damage as an end result.[18] For maculopapular rash and livedoid reticulopathy, enodothelium of blood vessels is the target.

Presence of virus in skin tissue in itself is a more sinister sign for viremia; and when coupled with complement-based deposits, it demands more extensive autoimmune work up including anti-nuclear antibodies (ANA) and anti-phospholipid antibodies (APLA) levels.

Figure 1


ChAdOxIn CoV-19 vaccine (Covishield) containing 5x10[10] viral particles
Introduced in the body in a dose of 0.5 ml
Triggers immune reaction
Antigen presenting cells
T-cell activation (Increased CD-8 T cells)
B- cell activation
Formation of antibodies and memory cells against SARS Cov-2 virus spike protein
Protection from infection and disease
Triggers
1. Genetic predisposition
2. Superimposed infection
3. Nutritional factors (de-regulated autophagy)
4. Physical or environmental factors
5. Hormonal factors
Antibody dependent enhancement of virus (sub-neutralising antibodies)
Antigenic components and haptens increase in the blood
As it is a newly developed vaccine, it may contain some foreign antigens
Activates complement and formation of antigen antibody complexes
Formation of antigen-antibody complexes
Cross react with human tissues
Bind to ACE – 2 receptors present in the spleen, lung, skin and endothelium mimicking Covid- 19 infection
Mimic natural Covid -19 infection
Molecular mimicry
Auto-immunity

Management

Standard management for patients with autoimmune cutaneous manifestations has not been defined currently. We have made a brief attempt to give a layout in the individuals at risk, precautions and preventions that can be taken along with required investigation and symptomatic management of the patients.

INDIVIDUALS AT RISK	PRECAUTIONS AND PREVENTIONS
Diabetes mellitus patients	Lifestyle modification respecting the circadian rhythm
Hypertensive patients	Avoidance of skipping of meals/prolonged starvations/ intermittent fasting beyond 3 months
Patients with Respiratory or Cardiovascular illness	Managing stress well
Patients with previous history or family history of autoimmune disorders	Doing physical activity on daily basis
Patients with skin lesions suggestive of vasculitis or autoimmune disorder during acute covid-19 infection or ICU admissions	Correction of underlying macro and micronutrient deficiencies like proteins, vitamin D, B12 and iron levels and serum ferritin

Recommended investigations

Individuals who have active infection or history of covid infection or with active cutaneous lesions suggestive of vasculitis are recommended to take the following tests for a detailed evaluation.

- SARS-Cov2 Antibody levels (Abnormalities in acute phase reactants)
- C-reactive protein
- D-dimer levels
- Vitamin B12 levels
- Iron studies with serum ferritin levels
- Fibrinogen, and low complement levels may also play a role, possibly through an autoimmune mechanism
- Skin biopsy

Such individuals when given vaccination might have higher risk of developing autoimmune disease.

CONCLUSION

We do not intend to deflate the overwhelming benefits of mass vaccination against SARS-Cov-2 virus and preventing the morbidity and mortality caused by it. We support the covid-19 vaccination globally to create immune barrier among the population. This article highlights the importance creating awareness and staying vigilant for the appearance of any new autoimmune disease and exacerbation of existing disorder and its management in light of increasing protecting antibodies against Covid 19 vaccination program and for future course of action for choice of vaccination and booster doses.

Covid scenario and mass vaccination has totally changed the understanding of dermatological disorders. We as physicians need to be more vigilant with any autoimmune disease presenting in our outpatient department, hence a detailed history of vaccination along with type of vaccine should be taken along with patient reassurance.

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FIGURES

FIGURE A: multiple well defined itchy, reddish- violaceous firm papules and plaques in photosensitive distribution signifying DLE-LP overlap

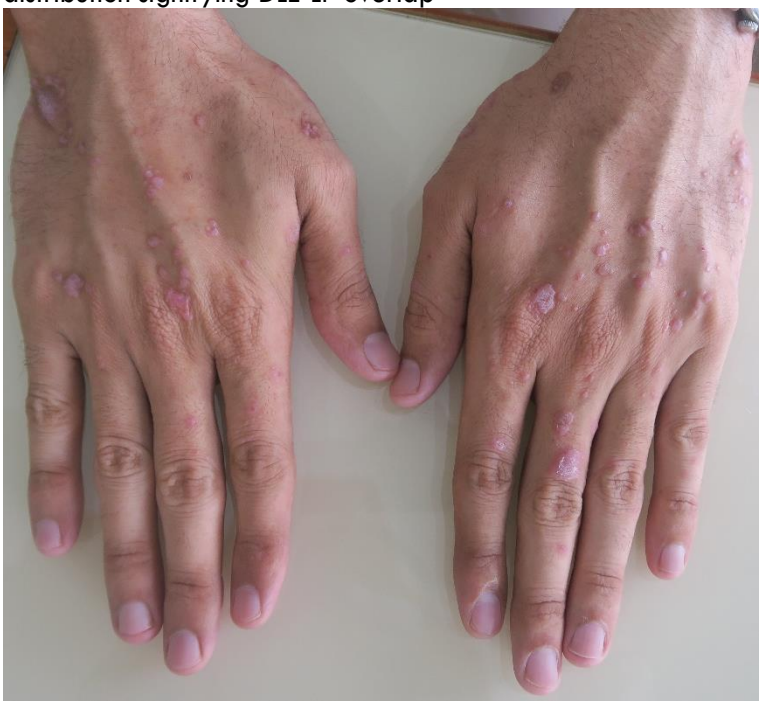

FIGURE B: multiple, itchy maculopapular eruptions

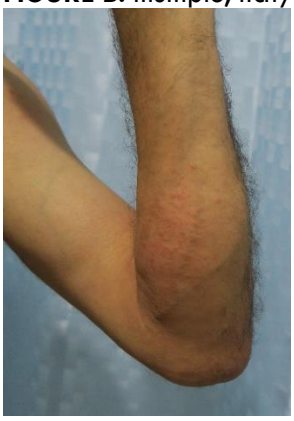

FIGURE C: single well-defined depigmented macule with leukotrichia denoting focal vitiligo

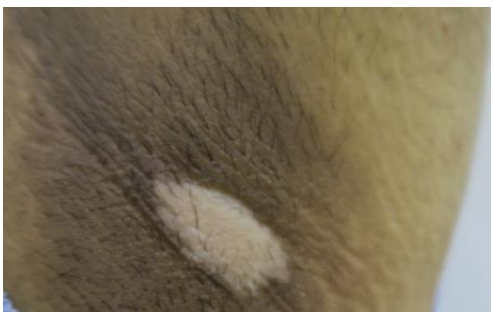

FIGURE D: multiple polygonal -violaceous plaques of lichen planus

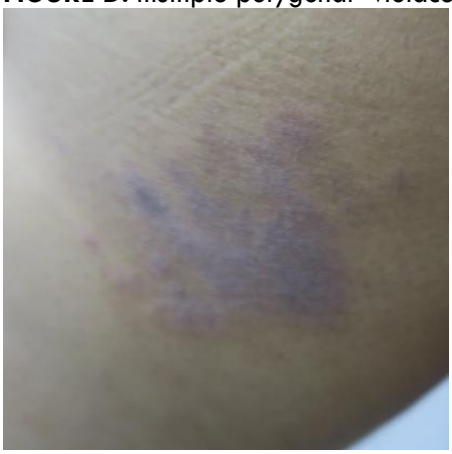

FIGURE E: single well-defined patch of alopecia areata

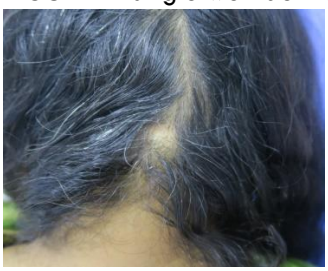

FIGURE F: single well-defined violaceous plaque and wickham's striae

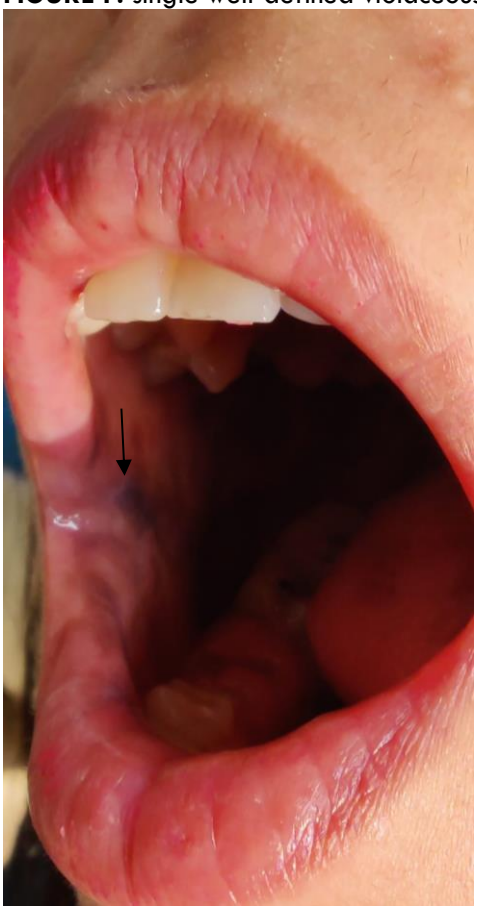

Figure G: Before and after images of exacerbation of existing stable vitiligo, new lesions extremely itchy and marked redness along the spreading margins

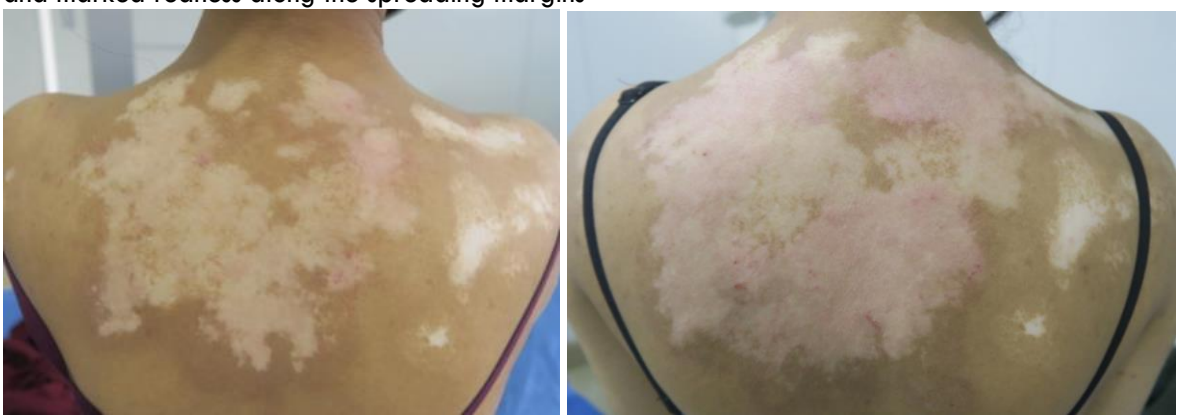

FIGURE H (a): Dermoscopy demonstrating follicular plugging and atrophy seen in discoid lupus erythematosus, (b) Follicular plugging, perifollicular halo, linear vessels c) structureless white areas, linear vessels, atrophy