COVID-19 Vaccine Associated Cutaneous Lymphomatoid Reactions

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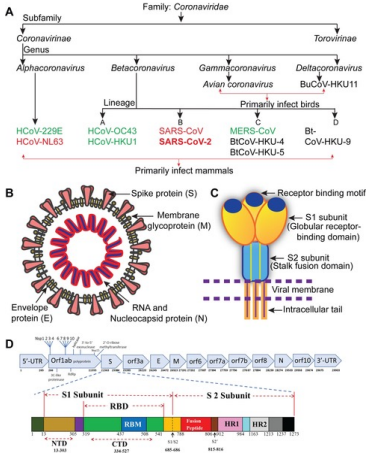
COVID-19 VACCINE

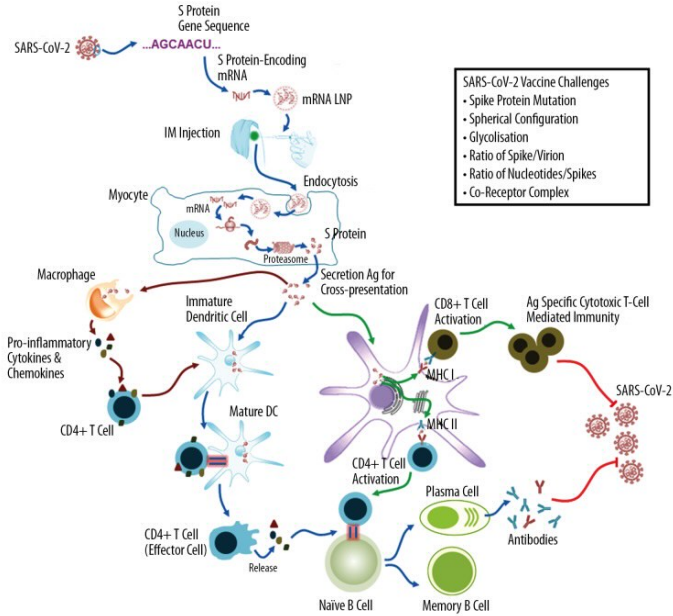
- Although there were nearly 50 candidate vaccines in clinical testing ultimately three became approved by the FDA with most patients receiving the Moderna or Pfizer vaccine
  - Moderna/NIAID – Nucleoside-modified messenger RNA that encodes the full length of SARS-CoV-2 spike (S) protein (mRNA-1273)
  - Pfizer/BioNTech – Nucleoside-modified messenger RNA that encodes the full of the SARS-CoV-2 spike protein (BNT162b2)
  - Janssen(Johnson and Johnson) – modified adenovirus (Ad26) encodes full length S protein (Ad26.COV2.S)

Fig 3. Classification and structure of coronavirus.



Mittal A, Manjunath K, Ranjan RK, Kaushik S, Kumar S, et al. (2020) COVID-19 pandemic: Insights into structure, function, and hACE2 receptor recognition by SARS-CoV-2. PLOS Pathogens 16(8): e1008762. https://doi.org/10.1371/journal.ppat.1008762
https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1008762

PLOS PATHOGENS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Myocyte
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Macrophage
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Cross-presentation
Immature
Dendritic Cell
Pro-inflammatory
Cytokines &
Chemokines
CD4+ T Cell
Mature DC
CD8+ T Cell
Activation
Ag Specific Cytotoxic T-Cell
Mediated Immunity
MHC I
MHC II
SARS-CoV-2
CD4+ T Cell
Activation
Plasma Cell
Antibodies
CD4+ T Cell
(Effector Cell)
Release
Naïve B Cell
Memory B Cell
SARS-CoV-2 Vaccine Challenges
• Spike Protein Mutation
• Spherical Configuration
• Glycolisation
• Ratio of Spike/Virion
• Ratio of Nucleotides/Spikes
• Co-Receptor Complex

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Clinics in Dermatology (xxxx) xxx, xxx–xxx

Clinics in Dermatology

The histologic and molecular correlates of COVID-19 vaccine-induced changes in the skin

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Abstract A total of 22 patients who had developed an adverse cutaneous reaction to the Moderna or Pfizer vaccine underwent biopsies. Each patient was assessed light microscopically, and, in select biopsies, spike glycoprotein and cytokine assessment were also conducted. The patients developed self-limited cutaneous reactions often described clinically as urticarial or eczematous within 1 day to 4 weeks after receiving the first or second dose of the Pfizer or Moderna vaccine. Classic clinical and morphologic depictions of type IV cutaneous hypersensitivity with features of eczematous dermatitis, interface dermatitis, granulomatous inflammation, and/or lymphocytic vasculitic component were observed. Clinical and/or histologic features of perniosis, pityriasis rosea, pityriasis rubra pilaris, and guttate psoriasis were seen in select cases. In 2 cases the dominant picture was urticarial vasculitis, possibly reflective of an Arthus type III immune complex action. The biopsy specimens of normal skin post vaccine and of skin affected by the post-vaccine eruptions showed rare deep microvessels positive for spike glycoprotein with no complement deposition contrasting with greater vascular deposition of spike protein and complement in skin biopsies from patients experiencing severe coronavirus disease 2019 (COVID-19). It is concluded that self-limited hypersensitivity reactions to the vaccine occur possibly owing to a substance found in the vaccine vehicle (eg, polyethylene glycol). An immune response that is directed against human-manufactured spike has to be considered because some of the reactions clinically and or histologically closely resemble mild COVID-19. Finally, vaccine-associated immune enhancement largely attributable to the adjuvant properties of the vaccine may unmask certain inflammatory milieus operational in psoriasis, atopic dermatitis, and subclinical hypersensitivity.

Published by Elsevier Inc.

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https://doi.org/10.1016/j.clindermatol.2021.07.011
0738-081X/Published by Elsevier Inc.

Please cite this article as: C. Magro et al., The histologic and molecular correlates of COVID-19 vaccine-induced changes in the skin, Clinics in Dermatology, https://doi.org/10.1016/j.clindermatol.2021.07.011.

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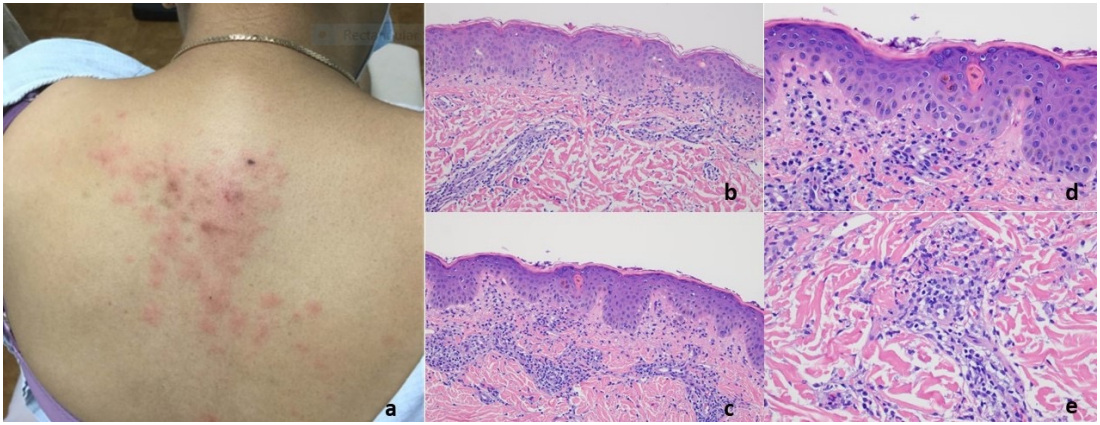
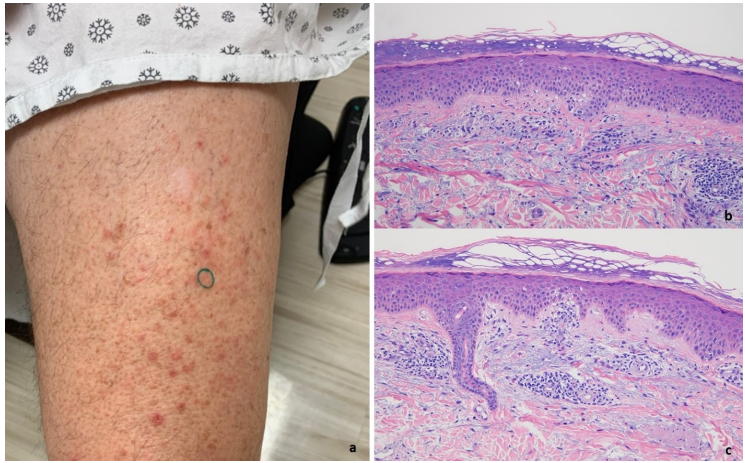
Results

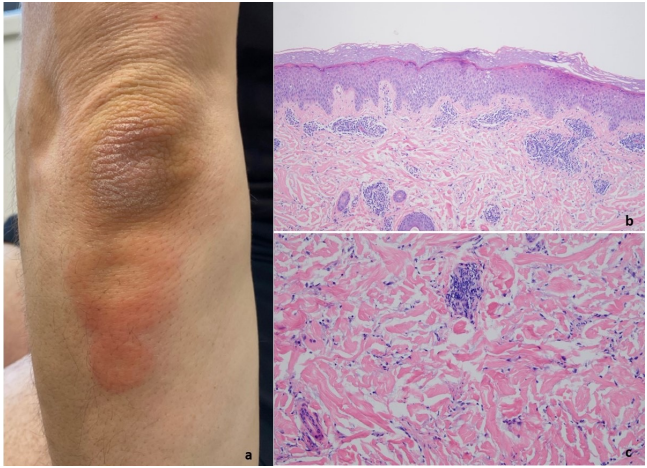
- Classic clinical and morphologic depictions of type IV cutaneous hypersensitivity with features of eczematous dermatitis, interface dermatitis, interstitial granulomatous inflammation, and/or granulomatous and or lymphocytic vasculitic component
- Clinical and/or histologic features of perniosis, pityriasis rosea, pityriasis rubra pilaris, and guttate psoriasis
- Leukocytoclastic vasculitis, possibly reflective of an Arthus type III immune complex action
- Biopsy specimens of normal deltoid (standard site for assessing for systemic complement pathway activation) skin post vaccine and of skin affected by the post-vaccine eruption showed rare deep microvessels positive for spike glycoprotein with no complement deposition contrasting with greater vascular deposition of spike protein and complement in deltoid skin biopsies from patients experiencing severe COVID-19.
- These reactions developed within 48 hours up to 4 weeks after the first or second dose of Pfizer or Moderna vaccine.



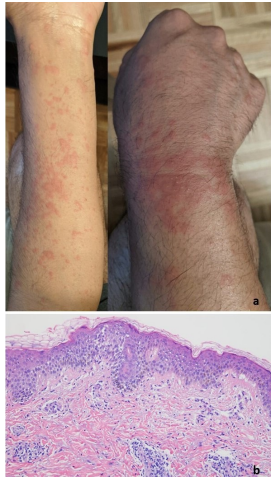
Type IV T-cell response with features of interface dermatitis and interstitial granulomatous inflammation (case 1). The patient was a 38-year-old woman who presented with blanchable erythematous papules (reproduced with permission from Dr. Henry J. Lee, New York, NY). The patient had received a COVID-19 vaccine, either the Moderna or the Pfizer, on February 15, 2021. (B, C) The biopsy showed a lymphocyte-mediated interface dermatitis associated with focal areas of epidermal attenuation. Lymphocyte satellitosis is visible around injured keratinocytes. (D) Focal areas of interstitial granulomatous inflammation accompanied by some degree of mesenchymal mucin deposition were observed. COVID-19, coronavirus disease 2019.(E)



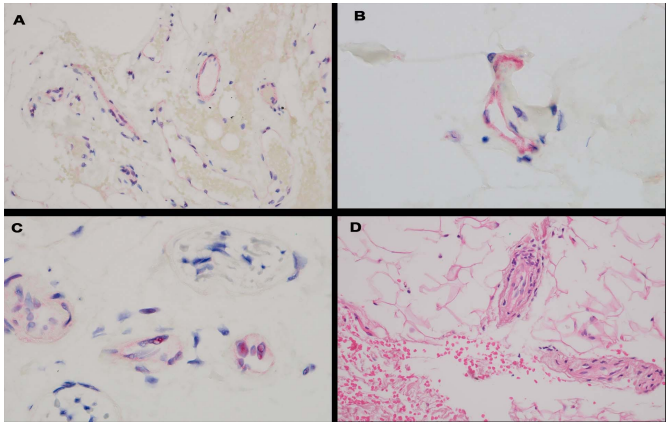
T-cell–mediated cytotoxic interface dermatitis (case 5). A 67-year-old man presented with a 2-week history of pruritic eruption on the trunk and extremities. The patient received the first and second doses of the Moderna vaccine on January 15, 2021 and February 16, 2021, respectively. (A) He developed an itchy eruption after the second dose (reproduced with permission from Dr. Silvia Mancebo, New York, NY). (B, C) The histologic findings are those of a classic morbilliform type IV hypersensitivity reaction combining delayed dermal hypersensitivity with a very mild cytotoxic interface dermatitis



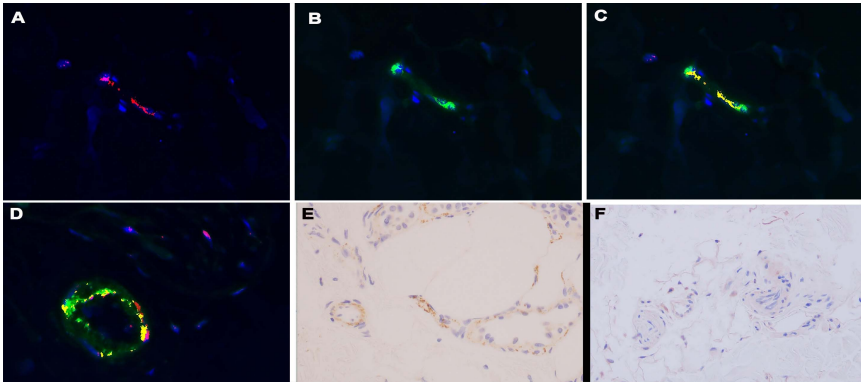
T-cell response predominated by eczematous features (case 16). (A) The patient is a 37-year-old man who developed an eruption that began on the elbows in February of 2021 and then subsequently spread to the knees (*reproduced with permission from Dr. Andrew Avarbock, New York, NY*). The eruption on the elbows and knees improved, but subsequently spread to the lower legs. (B) The epidermal changes are predominated by eczematoid alterations, but a subtle interface dermatitis is also noted. (C) The dermal component exhibits features of delayed dermal hypersensitivity characterized by vasocentric lymphocytic and eosinophilic infiltrates along with an interstitial granulomatous component.



T-cell response predominated by eczematous features (case 6). (A) A 34-year-old man presented with papulovesicular eruptions on the extremities, hands, and palms 1 week after receiving the Moderna vaccine (reproduced with permission from Dr. Paul Dantzig, New York, NY). The patient was treated with prednisone 60 mg daily, and the eruption cleared 3 days later. The biopsy showed intercellular edema within the epidermis along with lymphocytic exocytosis. A concomitant interface dermatitis was identified as evidenced by basilar vacuolar change with a few lymphocytes present along the dermal-epidermal junction. (B) Scattered eosinophils are noted.



Normal deltoid skin in patients with fatal COVID-19 versus healthy patients after vaccination. (A) In both deltoid skin samples from patients with fatal COVID-19 versus healthy patients after vaccination, there are a relatively greater number of positive staining vessels for ACE2 in the deeper dermis and in subcutaneous fat compared with the microvessels present superficially (red chromagen, 200 ×). The ACE2 distribution pattern mirrors spike glycoprotein endothelial cell localization. (B) Granular deposition within the endothelium for spike glycoprotein was present in the setting of fatal COVID-19 (red chromagen, 1000 ×). (C) A similar pattern of endothelial cell staining for spike glycoprotein was noted in the post-vaccine biopsy (red chromagen, 1000 ×). (D) A microvessel after vaccine in which a mononuclear cell response is evident (hematoxylin and eosin, 1000 ×). ACE2, angiotensin converting enzyme 2; COVID-19, coronavirus disease 2019.



Patients with normal deltoid skin after vaccination shows endothelial cells activated by the spike protein. (A) Using the Nuance software, a microvessel positive for spike glycoprotein using a red chromagen gives a red signal localized to endothelium (red chromagen, 1000 ×). (B) The same microvessels show a green signal in a similar distribution highlighting interleukin 6, using a diaminobenzidine stain (diaminobenzidine, 1000 ×). (C) The combined signal fluoresces yellow, proving colocalization of spike glycoprotein and interleukin 6 in the biopsy of a person post-vaccination (1000 ×). (D) Panel demonstrates a similar strong coexpression between the spike protein and caspase 3 in a post-vaccine biopsy specimen (1000 ×). (C) An extensive microvascular deposition of C5b-9 is visible in a case of severe COVID-19 (diaminobenzidine, 400 ×). (F) In contrast, the post-vaccine sample does not show significant complement deposition (diaminobenzidine, 400 ×). COVID-19, coronavirus disease 2019.

What is the basis of these vaccine triggered reactions in the skin ?

Pathophysiology of the vaccine associated reactions

- An adaptive T or B cell immune response to spike glycoprotein although as a generalized immune response given the small amount of human synthesized spike in skin samples
- A type IV immunologic response to a component of the vaccine vehicle
- Unmasking of subclinical cutaneous eruptions with a genetic component (psoriasis/atopic eczema) or subclinical hypersensitivity due to immune boosting properties of the vaccine

Pathophysiology of the type IV immune reactions: The role of superantigens and the preferential follicular helper T cell response

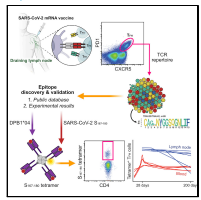
- The pattern of interface and interstitial granulomatous dermatitis with granulomatous/lymphocytic vasculitis is among the commonest histologic COVID-19 vaccine reaction patterns and is also typical hypersensitivity reactions triggered by microbial pathogens with superantigen properties(Magro CM et al, 1998).
- Spike glycoprotein has potent superantigen properties and therefore can stimulate a significant component of the T cell repertoire(Cheng MH et al, 2020).
- Spike glycoprotein induces a robust follicular helper T cell response(Mudd PA et al, 2022)

Cell

Article

SARS-CoV-2 mRNA vaccination elicits a robust and persistent T follicular helper cell response in humans

Graphical abstract



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In brief

Analysis of draining lymph nodes of individuals vaccinated with BNT162b2 mRNA vaccine against SARS-CoV-2 identifies viral-spike-specific follicular helper CD4+ T cells that persist for months and contribute to long-term immunity.

Highlights

- SARS-CoV-2 vaccines induce robust human T_{FH} cell responses in draining lymph nodes
- HLA-DPB1*04 restricts the immunodominant SARS-CoV-2 $S_{167-180}$ epitope
- $S_{167-180}$ is recognized by T cell receptors with a public α-chain motif
- S-specific T_{FH} cells are maintained in draining lymph nodes 6 months after vaccination

Mudd et al., 2022, Cell 185, 603–613
February 17, 2022 © 2021 Elsevier Inc.
https://doi.org/10.1016/j.cell.2021.12.026

Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation

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Contributed by Ivet Bahar, June 29, 2020 (sent for review May 26, 2020; reviewed by Talal A. Chatila, Ruth Nussinov, and Celia A. Schiffer)

Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 is a newly recognized condition in children with recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. These children and adult patients with severe hyperinflammation present with a constellation of symptoms that strongly resemble toxic shock syndrome, an escalation of the cytotoxic adaptive immune response triggered upon the binding of pathogenic superantigens to T cell receptors (TCRs) and/or major histocompatibility complex class II (MHCII) molecules. Here, using structure-based computational models, we demonstrate that the SARS-CoV-2 spike (S) glycoprotein exhibits a high-affinity motif for binding TCRs, and may form a ternary complex with MHCII. The binding epitope on S harbors a sequence motif unique to SARS-CoV-2 (not present in other SARS-related coronaviruses), which is highly similar in both sequence and structure to the bacterial superantigen staphylococcal enterotoxin B. This interaction between the virus and human T cells could be strengthened by a rare mutation (D839Y/N/E) from a European strain of SARS-CoV-2. Furthermore, the interfacial region includes selected residues from an intercellular adhesion molecule (ICAM)-like motif shared between the SARS viruses from the 2003 and 2019 pandemics. A neurotoxin-like sequence motif on the receptor-binding domain also exhibits a high tendency to bind TCRs. Analysis of the TCR repertoire in adult COVID-19 patients demonstrates that those with severe hyperinflammatory disease exhibit TCR skewing consistent with superantigen activation. These data suggest that SARS-CoV-2 S may act as a superantigen to trigger the development of MIS-C as well as cytokine storm in adult COVID-19 patients, with important implications for the development of therapeutic approaches.

COVID-19 | superantigen | SARS-CoV-2 spike | toxic shock syndrome | TCR binding

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, is a betacoronavirus (β-CoV) closely related to SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV (1). COVID-19 can manifest in adults as a severe interstitial pneumonia with hyperinflammation, while severe respiratory manifestations are rare in children (2–4). Recently, however, multisystem inflammatory syndrome in children (MIS-C) has been observed in patients that either tested positive for COVID-19 (by PCR or serology) or had epidemiological links to COVID-19 (5–7). After initial reports in the United Kingdom (5), many cases have been reported in Europe (6, 7) and New York (Centers for Disease Control and Prevention). However, no such cases have been reported in China, Japan, or South Korea, which have also been severely impacted by the COVID-19 pandemic. MIS-C shock syndrome (TSS) (8, 9) (Table 1), rather than Kawasaki disease (KD), due to marked demographic, clinical, and laboratory differences (6). Indeed, a recent uncontrolled retrospective case study concluded that MIS-C is distinct from KD and KD shock syndrome (10). The similarities to TSS and the association of MIS-C with COVID-19 led us to hypothesize that SARS-CoV-2 may possess superantigenic fragments that induce an inflammatory cascade and may also contribute to the hyperinflammation and cytokine storm observed in severe adult COVID-19 patients (3, 4). The question we raised is, does SARS-CoV-2 spike (S) possess superantigenic fragments that could elicit such reactions upon binding proteins involved in the host cell cytotoxic adaptive immune response? Such a reaction was not observed in the SARS-CoV pandemic of 2003 (SARS1 hereafter). What is unique to SARS-CoV-2, and how might recent mutations in SARS-CoV-2 S have promoted such an increased virulence?

TSS can be caused by two types of superantigens (SAgs): bacterial or viral. Bacterial SAgs have been broadly studied. They include proteins secreted by *Staphylococcus aureus* and *Streptococcus pyogenes* that stimulate massive production of

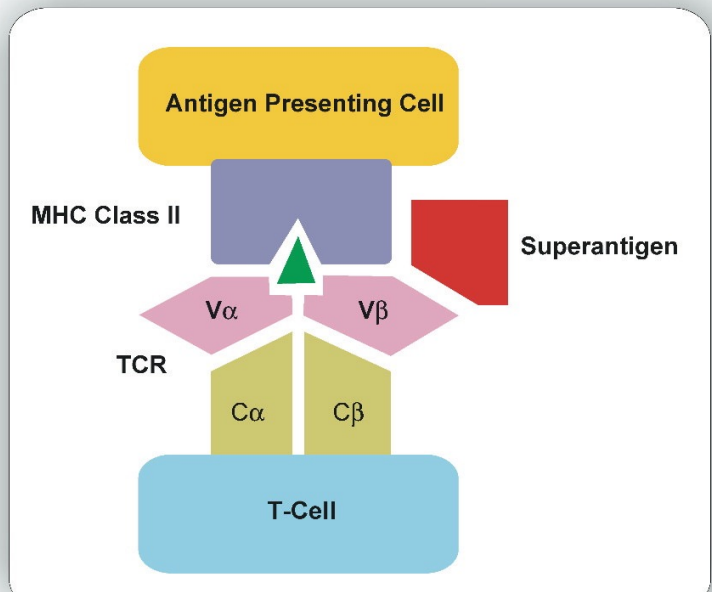
Significance

A hyperinflammatory syndrome reminiscent of toxic shock syndrome (TSS) is observed in severe COVID-19 patients, including children with Multisystem Inflammatory Syndrome in Children (MIS-C). TSS is typically caused by pathogenic superantigens stimulating excessive activation of the adaptive immune system. We show that SARS-CoV-2 spike contains sequence and structure motifs highly similar to those of a bacterial superantigen and may directly bind T cell receptors. We further report a skewed T cell receptor repertoire in COVID-19 patients with severe hyperinflammation, in support of such a superantigenic effect. Notably, the superantigen-like motif is not present in other SARS family coronaviruses, which may explain the unique potential for SARS-CoV-2 to cause both MIS-C and the cytokine storm observed in adult COVID-19.

Author contributions: M.H.C., M.A., and I.B. designed research; M.H.C., S.Z., R.A.P., L.P., E.W., M.B., M.A., and I.B. performed research; M.H.C., S.Z., R.A.P., M.N.R., M.B., M.A., and I.B. analyzed data; and M.H.C., R.A.P., M.A., and I.B. wrote the paper.

Reviewers: T.A.C., Children's Hospital Boston; R.N., Frederick National Laboratory; and C.A.S., University of Massachusetts Medical School.

Competing interest statement: Patent filing process has been started for short peptide sequences to neutralize the superantigenic fragment.


Antigen Presenting Cell
MHC Class II
Superantigen
Vα
Vβ
TCR
Cα
Cβ
T-Cell

The T Cell lymphomatoid reactions in the setting of the COVID-19 Vaccine

Three cases have been encountered in the routine and consultative practice at Weill Cornell Medicine where these apparent vaccine reactions appeared atypical cytomorphologically, architecturally and phenotypically.

A 35 year old male who developed primary cutaneous CD4+ small medium sized T cell lymphoproliferative disease 1 week after the first dose of the Pfizer vaccine.

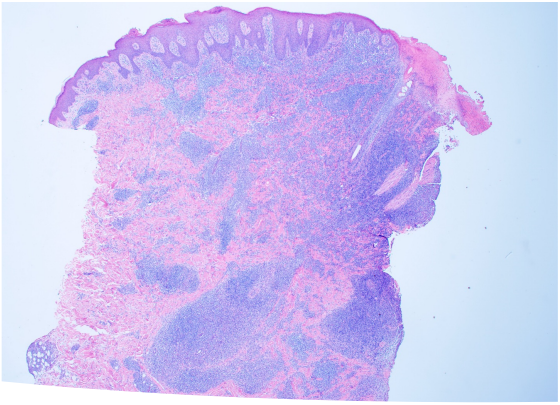
A 18 year old male who developed LYP within 1 month following the second dose of the Pfizer vaccine, responding to MTX and then recurring when he had a COVID-19 break through infection.

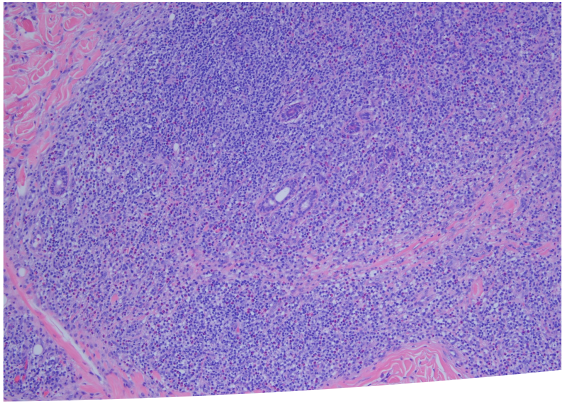
A 63 year old female who developed CD8+ CD25+ peripheral T cell lymphoma NOS after the second dose of the Pfizer vaccine

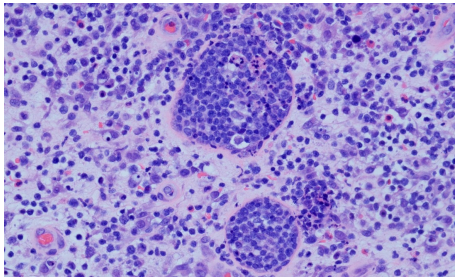
Prior reported cases include recurrent CD30+ primary cutaneous LPD(2 days after first dose of Pfizer in a 79 year old male)(Brumfiel et al,2021), the progression of AILD(Goldman S et al,2021)(66 year old male developing AILD within 5 months of receiving the Pfizer and then worsening of the AILD with the booster

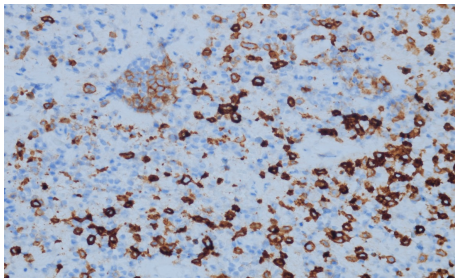
Clinical History

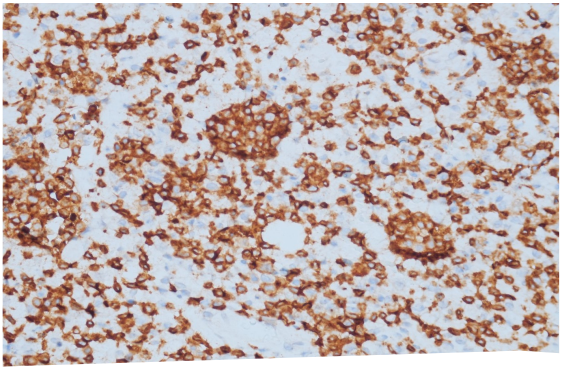
- 18-year-old healthy male who abruptly developed a papular nodular skin rash in his right axilla after he received the second SARS-CoV-2
- The lesions began as a singular nodule, which then diminished with the development of multiple others within the same location
- He later developed an oval pink papule on his left thigh
- Both were biopsied as LYP overlapping type A and type C
- Began methotrexate with improvement, and stopped due a mononucleosis infection while at college
- Was doing well without lesions, until a recent COVID-19 infection where he then developed new pink crops of papules on the shaft of his penis
- He was restarted on methotrexate

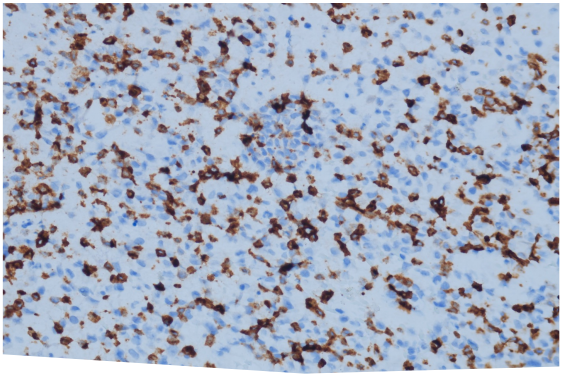












• CD7

Clinical history

- 35-year-old male with no significant past medical history developed a nodule on his forehead 1 week after his first dose of the Pfizer-BioNTech COVID-19 vaccine
- The lesion was stable and otherwise asymptomatic for 3 months, and the patient had no systemic symptoms
- Physical examination revealed a 0.5 x 1.0 cm non-tender, non-ulcerated nodule on the mid forehead
- A punch biopsy was performed
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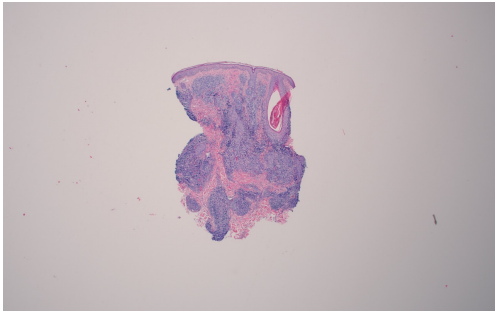
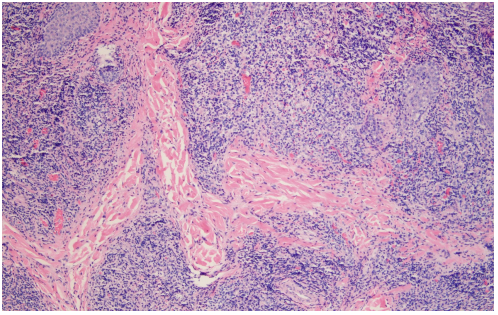
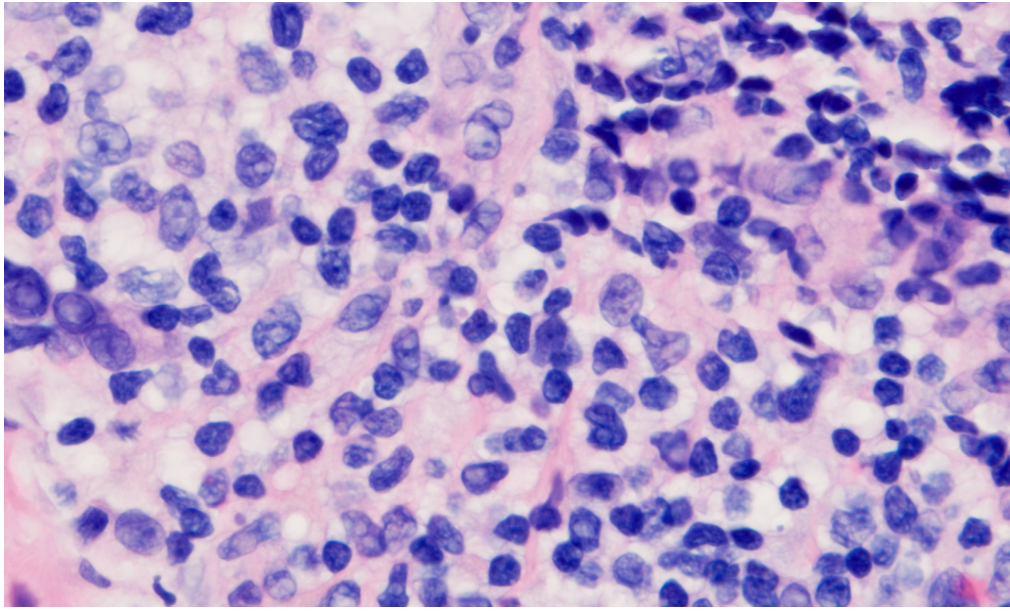
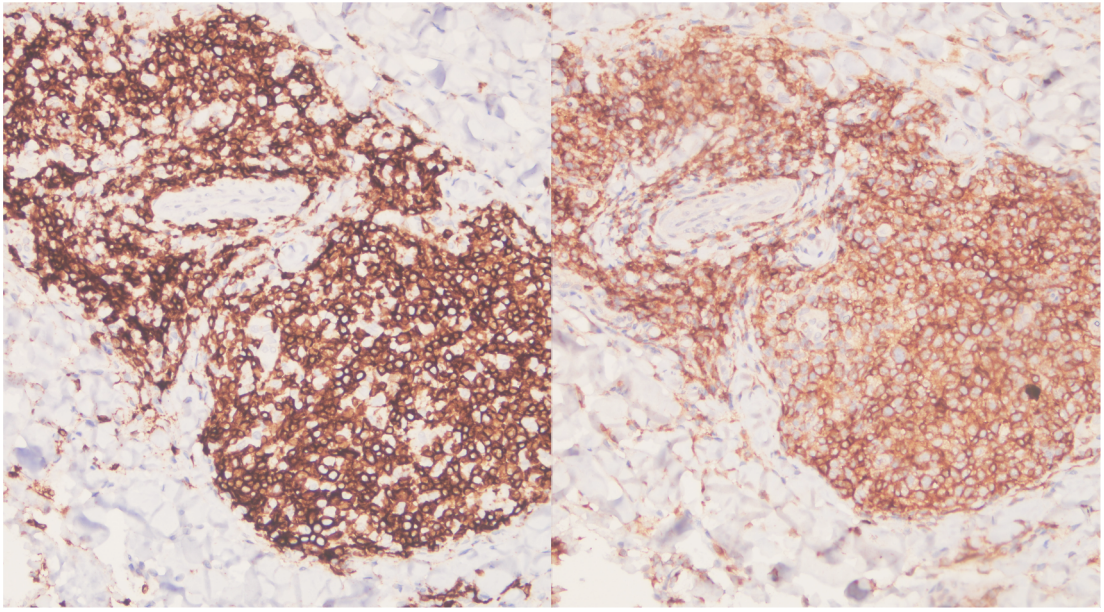
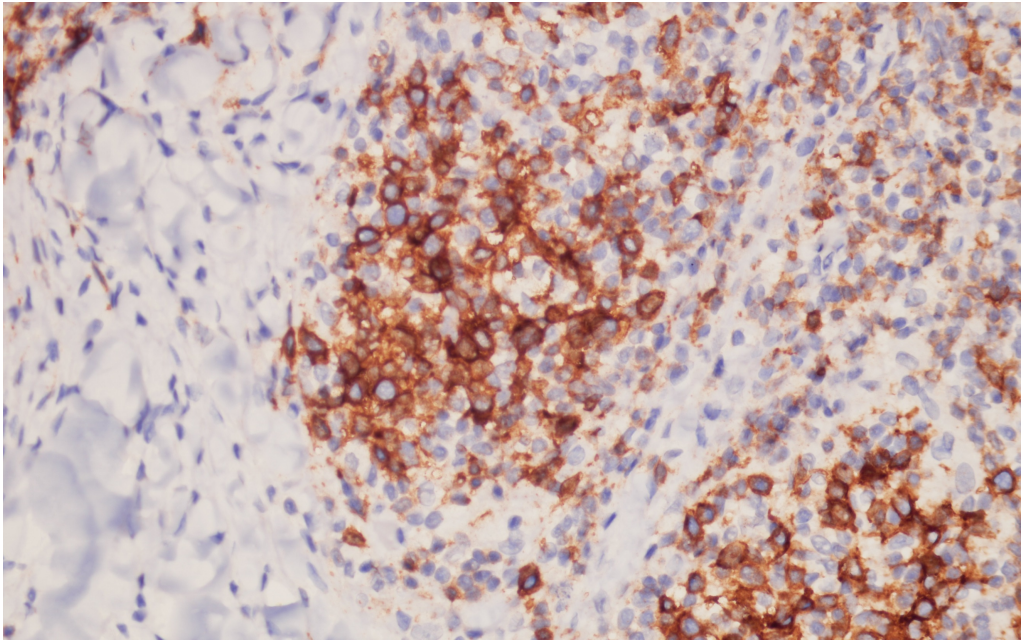










Case of post vaccine PTCL, NOS

63-year-old female with hypertension developed a non-itching rash on her bilateral arms and legs after her 2nd Pfizer COVID-19 vaccine.

The initial biopsies in April/May were interpreted as a delayed hypersensitivity reaction followed by a biopsy in June 2021 interpreted as probable hypersensitivity but with atypical lymphomatoid features versus an evolving T cell LPD.

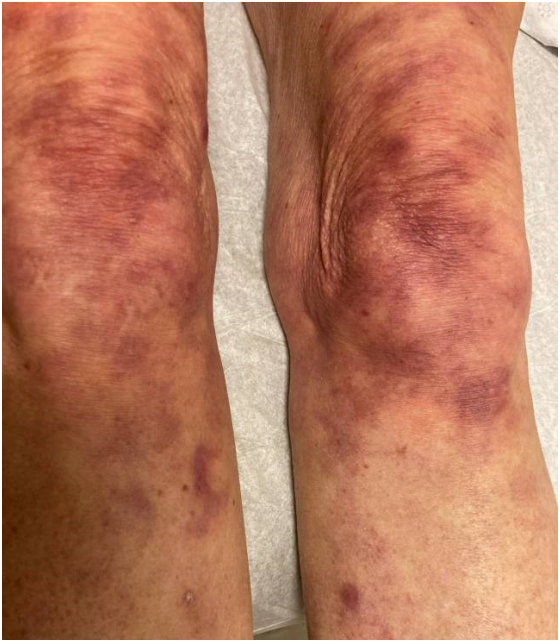
The rash resolved after systemic corticosteroids

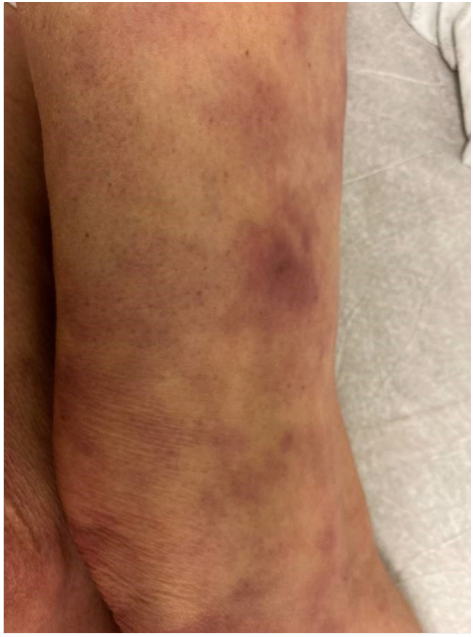
The patient developed erythematous patches on her face, extremities and trunks after she received the vaccine booster

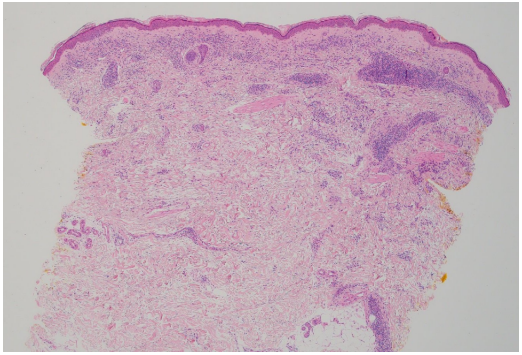
Again, systemic corticosteroids succeeded in resolving the rash

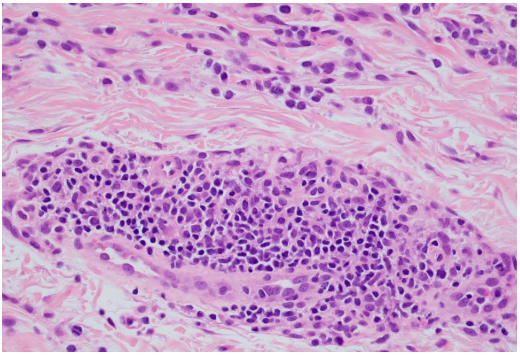
The patient then had breakthrough COVID and quickly recovered, however she developed new violaceous patches, plaques as well as nodules(November 2021, biopsies were performed on patches and nodules)

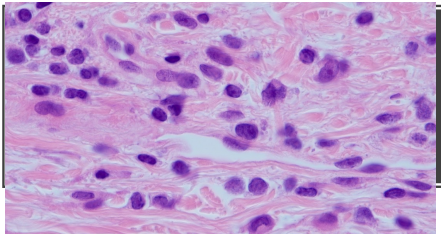
She has continued to develop new skin lesions and now has extracutaneous lymph node involvement.





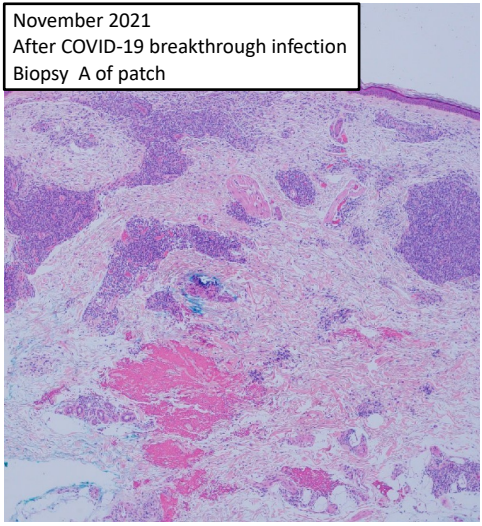


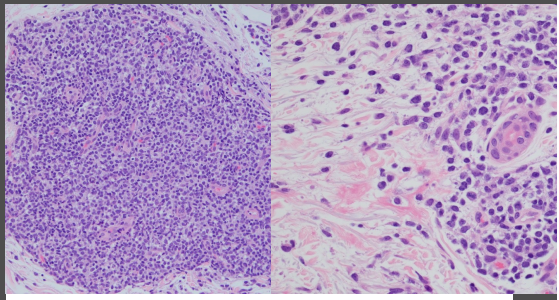


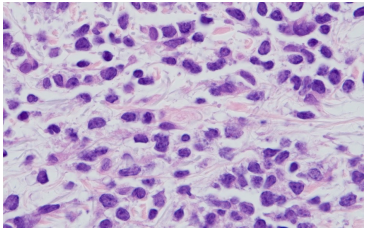


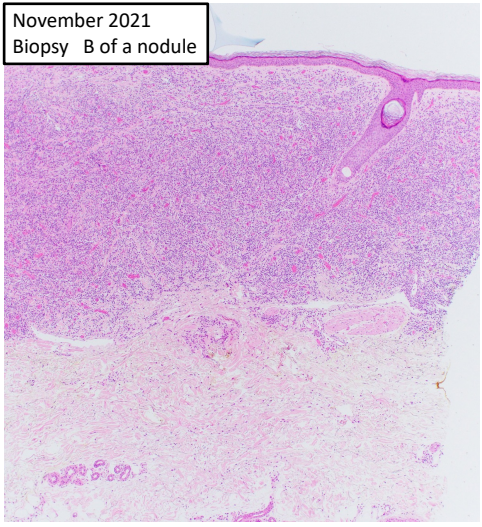
Initial Set of Biopsies in June 2021

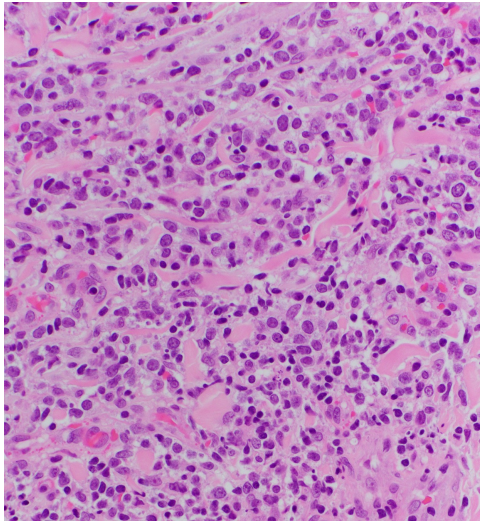
November 2021
After COVID-19 breakthrough infection
Biopsy A of patch

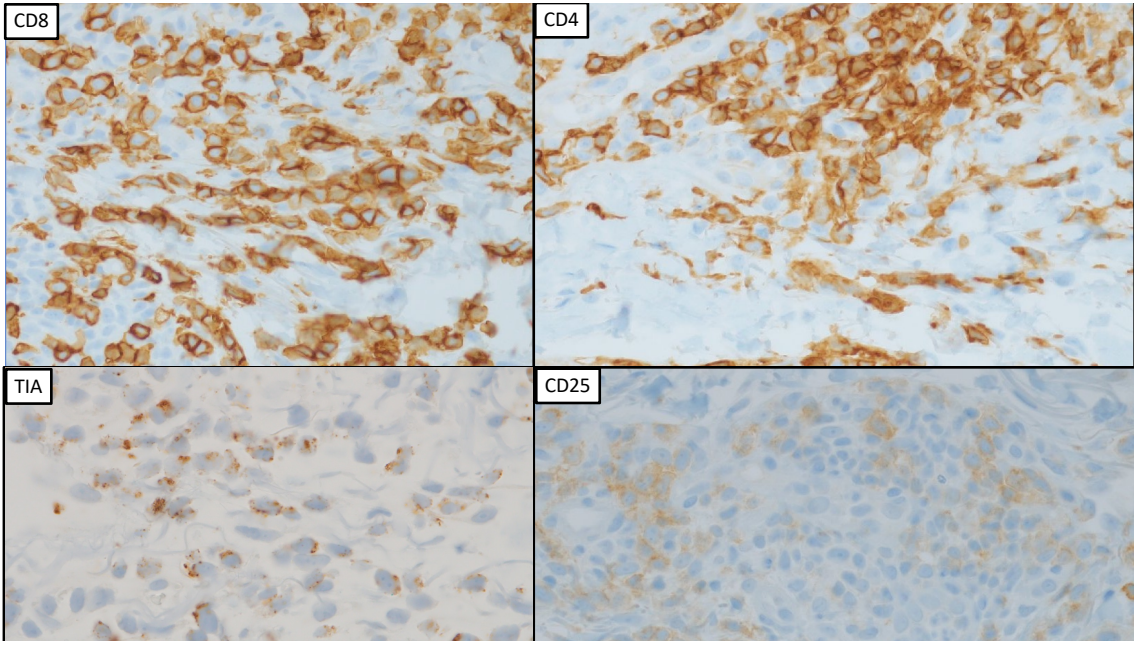







November 2021
Biopsy B of a nodule




CD8
CD4
TIA
CD25

Summary of Light Microscopic Findings

- Progression of an initial type IV immune response to the vaccine to a progressive atypical lymphomatoid process whereby throughout the biopsies there was evidence of an identical T cell clone and a rare unique T cell was implicated namely a CD8+ or double CD25+ positive non-regulatory cytotoxic CD8+ memory T cell.
- Earlier biopsies could be interpreted as a vaccine triggered CD8+ T cell lymphoproliferative disorder of non-regulatory CD8+ memory T cell origin.
- Subsequent biopsies showed progression to overt lymphoma consistent with a CD8+ positive peripheral T cell lymphoma of non-regulatory CD8+ memory T cell origin as a unique form of immunosenescent lymphoma, NOS.

Is there a benign T cell Counterpart that could be preferentially expanded in response to spike glycoprotein in the middle aged to older age setting?

IL2/IL4 producing CD8+CD25+ non-regulatory memory T cells are seen in older patients with depleted naïve T cells

- A very rare T cell subset is represented by an IL-2/IL-4-producing CD8+CD25+ non-regulatory memory T cell population that occurs in a subgroup of healthy elderly persons who have depleted naïve T cells ; these CD8 positive T cell can show a double positive phenotype(Herndler-Brandstetter et al 2005).
- This cell population represents a critical reservoir for launching an intact immune response to viruses and to a vaccine; the presence of double positive memory T cells in fact has been correlated with a better outcome in patients with COVID-19(Kalpakci et al, 2020,(Nascimbeni et al 2004) .

How do we link the spike glycoprotein mediated type IV immune reactions to COVID-19 vaccine associated T cell Lymphoproliferative disease?

A multistep process involved in lymphomagenesis

Initial antigenic stimulus leads to a clonally restricted T or B cell response.

In the setting of underlying iatrogenic or endogenous immune dysregulation (underlying autoimmune disease or a genetic predisposition), an overzealous clonal immune response occurs.

Subsequent oncogenic transformation of clonally restricted T or B cells unrelated to any properties of the vaccine or virus eventuates in endogenous T/B cell lymphoproliferative disease.

The nature of the adaptive T cell response to spike glycoprotein could determine the type of vaccine associated LPD

- 1. In healthy patients especially younger patients a robust type IV immune response mediated by activated antigen specific CD4+ or cytotoxic CD8 T cells is characteristic (benign reaction is the typical type IV hypersensitivity vaccine reaction; atypical counterpart would be CD4+ CD30+ LYP).
- 2.Follicular helper T cells are also preferentially expanded by spike glycoprotein(atypical counterpart is primary cutaneous follicular helper T cell dyscrasia (i.e. primary cutaneous CD4+ small medium sized pleomorphic T cell LPD) and angioimmunoblastic lymphoma).
- 3. In older individuals where the naïve T cell repertoire is significantly diminished, expansion of CD25+CD8+ T cells occur in response to SARS CoV-2 and is protective against severe disease (atypical counterpart would be CD25+CD8+ PTCL NOS)