Student Section

Pathology Specialty Educational Booklet

April 2021

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Note from the Editor

After what has been a long and difficult year of lockdown, there seems to be some hope for normality in the horizon with falling infection rates and COVID-19 burden on hospitals. This is thanks to the tireless work of those on the frontline, whether it be ITU staff, laboratory professionals or those running the day-to-day activities that we all rely on. One particular field that has been quintessential to this progress is Pathologists. This includes histopathologists delivering and maintaining cancer services, virologists at the frontline of COVID-19 research and sequencing or immunologists identifying new treatment methods such as tocilizumab.

The pandemic has also changed student involvement and interaction with Pathology. This has especially affected those who were undertaking laboratory-based research projects and specialty placements in hospitals. In this booklet, we delve into the roles of such professionals, such as histopathologists and virologists to identify their day to day working pattern and their importance in the pandemic (pages 3 and 5). Recently, due to the variations in COVID-19 strains, certain unusual presentations have also been identified, such as skin manifestations, which are discussed on page 14. We have also included some revision resources for medical students to use to sharpen their knowledge on dermatopathology and gastroenterology (pages 9, 12). Finally, pages 7 and 11 also include articles on how immunology and basic science affect our day-to-day life and future research implications from this.

I hope that you will be inspired from this booklet to learn more about Pathology and the vast range of specialties it encompasses and be confident if faced with Pathology questions in exams.

On behalf of the RSM Student Section Core Committee,

Maiar Elghobashy, University of Birmingham

Editor

A Day in the Life of a Virologist: Dr Eleri Wilson-Davies

Written by Zain Ahmad, University of Exeter

Dr Eleri Wilson-Davies is a consultant medical virologist currently working at the Southampton specialist virology centre. She spoke to me about her journey to becoming a virologist, why she chose the specialty, her training, and the unique challenges of the job, especially during the current coronavirus pandemic.

What does a virologist do? Could you describe a typical week for you?

The biggest thing that depends on is whether there is a pandemic or not. So, it will probably be more useful to talk about what a usual week would be, rather than what it currently is, which I hope is a rather unusual situation. One of the wonderful things about virology is that it provides the opportunity to do a variety of very different areas of medicine. So, part of the week would be related laboratory medicine looking at the results, and then advising clinicians on treatment, diagnostics, which samples to take, management and infection control requirements for individual patients. Another part of the week involves being in clinic seeing patients.

I have an interest in stem cell transplantation patients, and immunocompromised patients particularly those who suffer from recurrent herpes simplex or varicella zoster viruses. These patients have recurrent episodes of shingles, so I help to manage this in the right way. The rest of the week will be spent doing research. This time is variable, but the majority of virologists will be involved in research, whether that be clinically based, in the lab, or epidemiological studies. Other roles include management and teaching. I teach a wide number of students, postgraduates, junior doctors, those completing specialty training and I even teach on a master's course. I think the variety is one of virology's huge advantages.

How has the COVID-19 pandemic impacted your work?

Obviously, most of the clinical queries we see now are COVID related. For example, in patients with low levels of SARS-CoV-2 RNA who have been in the wards for over the week, we have to think about whether it is an acquired infection or a past infection. It has also provided opportunities, for example, I am the principal investigator for the SIREN study which is looking at the risk of reinfection of SARS-CoV-2 in healthcare staff. Initial data indicates that there is an over 80% risk reduction of reinfection if someone has had a previous SARS-CoV-2 infection.

> ***"One of the wonderful things about virology is that it provides the opportunity to do a variety of very different areas of medicine"***

What was your training like?

I had a fantastic opportunity under Professor Bill Carman up in Glasgow, which is a particularly exciting place to train in virology. We had a lot of individuals who had hepatitis C coming in due to intravenous drug use. Bill Carman was one of the individuals who was at the forefront of moving medical virology from a cell culture-based specialty to a molecular based specialty. We produced PCR assays which provided an extraordinary service to patients in the west of Scotland. So,

it was a fantastic learning experience, and I'm sure London is similar in many ways perhaps with more HIV patients.

Why did you pick virology as a specialty?

I was interested in infection as a student. I think part of that intrigue was about the fact that you could actually cure things. However, from my time as a junior doctor working in genitourinary medicine, I was unsure that I wanted to go down that route to become an HIV doctor. I looked around and managed to get myself on a special study module, which gave me the opportunity to see what Professor Breuer was up to. Many individuals have that mentor that inspired them, and she was definitely that person for me. There is such a huge variety of jobs available in medicine, you can go into such a wide range of positions after your foundation training, the world is your oyster as to how you are going to spend your working life.

How would you describe your work life balance?

Excellent under normal circumstances, but the pandemic has changed that for very obvious reasons. In normal times, being in a small specialty, you will have a one in two or a one in three on calls but that is not particularly onerous, I was perfectly able to cope with that and have a family and bring up my children. This year, there have been nights where I have only had five or six hours left of sleep. However, pandemics do not happen every day and this one has gone on longer than the swine flu epidemic, but I would say under normal circumstances that your job isn't your entire life.

Has your current role met the expectations you had before you started your training?

I think it has. What I loved about seeing Professor Breuer at Barts, was seeing the opportunity to do academic work while maintaining clinical contact with patients. So, you are helping provide patients with good care and be a part of the research process. That was very important to me as I did not want to lose my clinical contact and what it meant to be a doctor. You have clinical medicine, laboratory medicine and research. That variety is quite unusual when it comes to medical specialties, and I love that I truly do.

What would you say has been the most rewarding moment in your career?

During the time of the Ebola epidemic, I had identified that dealing with hazard grade 4 pathogens in a containment level 3 laboratory (CL3), was capable of being done in a safe way. Not to culture the virus but to inactivate any presence of the virus and then perform PCR. I went through the enormous number of steps to try and push this idea through, I contacted all the statutory bodies involved and got agreement. Just before the Ebola epidemic took hold, I got agreement to perform testing for these viral haemorrhagic fevers (VHF) in a CL3, so we did not need a containment level 4 (CL4) lab. I managed to get the Scottish government to agree that we should be offering VHF testing up in Scotland. I was incredibly pleased when they funded the screening to take place, and now that is taking place in Edinburgh. This was a massive change. Previously samples in Glasgow were having to be driven down to Porton Down (near Salisbury). It would take a good 24 hours to find out if someone has a VHF or not, and this makes a huge difference. This was vital for sick patients up in Scotland, so that they could get the care they really needed. I was disappointed that I didn't get a chance to take part in the testing, nonetheless it would not have occurred were it not for my work.

"What I loved about seeing Professor Breuer at Barts, was seeing the opportunity to do academic work while maintaining clinical contact with patients. So, you are helping provide patients with good care and be a part of the research process"

What would you say are the most challenging aspects of your job?

I would say the challenge is the fact that you are working in a small group. The specialty is quite small, and I would say there aren't enough virologists, but I'm sure every consultant could say that about their specialty. But, when you are one of two or three virologists, it limits the opportunity to discuss other people's experiences. But the answer to that is that we in medical virology are very good at keeping in touch with each other, either through WhatsApp or through the UK clinical virology network (CVN). On the CVN discussion board we can put up a case and ask for other people's opinions about what they would do in that circumstance. Other people may know things that you have not come across before, so that is one way we get around the challenge of working in a small group.

Another issue would be that there are a smaller number of posts available across the country. So that means at least in the short term you have less say on where you want to work with these posts being available mainly in tertiary referral centres, which are university cities usually. But this isn't something that bothered me I was very happy to go where I had to go to do what I wanted to do. I do think that you need to have that mindset at the start, because jobs may open up closer to family later down the line, so you may have to move somewhere where you hadn't planned in the shorter term.

What would you say to a medical student that is interested in pursuing a career in virology?

I think it is an excellent option, whether you are interested in an academic career or if you want a mixture of clinical and laboratory medicine. I would say that those skills are vital in order to provide the right advice and management for the patients that we see. There is such a vast array of viruses, and their presentations are quite varied. We deal with other pathogens as well, usually things the microbiologists cannot grow we for example syphilis, chlamydia, and gonorrhoea. You also get to help some of the most vulnerable members of society, and hopefully get them through their treatment. So, I think there are massive advantages to medical virology, and I would highly recommend it.

If medical students are interested in virology, what things would suggest they do to learn more about the specialty?

I would just encourage anyone interested to get in touch with their local virologist(s) and even try to get involved in some audits or research, we always have plenty going on. Personally, directly after medical school I went into a master's degree in clinical microbiology. Doing something like this marks you out compared to others. As an undergraduate, I also got to be an author on a paper. These are all things I would recommend you do. It is important to have that time to work with somebody and see how they think, and if you get the chance make sure you join in on the clinics, and MDTs. I think if you do that you will have a great idea about whether this a specialty worth pursuing for you.

Histopathologists in cancer diagnosis and management

Written by Mirna Elghobashy, University of Birmingham

Introduction

Histology is a continuously changing field in medicine, driven by technological advancements and novel research (1). The role of a histopathologist is varied and ranges from dissecting macroscopic specimens obtained from surgery, analysing specimens microscopically and molecular analysis of tumours (2). Histopathologists are also vital members of the multi-disciplinary team meetings; their assessment of tumour grade, stage and response to biological therapy directly affects the prognosis and management of the patient (figure 1). Additionally, they play an integral role in screening programmes e.g. examining core biopsies in breast lumps (2). Although histopathologists have very little patient contact, the specialty has a significant impact on patient care, particularly with regards to diagnosis and management of cancer.

Diagnosis

During the initial management of a suspected malignancy, doctors will take samples from the suspected cancer site. After the samples are fixed, pathologists assess its general gross description, including dimensions, consistency and macroscopic abnormalities; this is particularly important in larger samples.

Following staining, the slides are analysed by histopathologists initially at low power then progressively higher power on microscopy. This provides information about the architecture of the biopsy specimen and general features of the tumour (3). This can include tumour margins (how close cancer cells are to the edge of the biopsy sample), pigmentation, cellularity, tumour components (proportion of stroma, fat and tumour

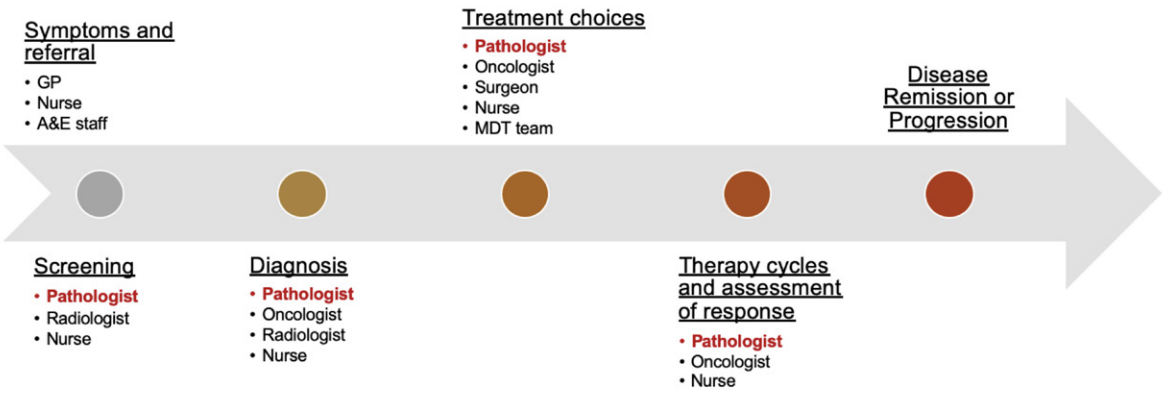


Figure 1: Diagram of a cancer patient's journey and the healthcare professionals involved in each stage. The pathologist is involved in almost every stage.

cells) and the presence of glands or tubules. On higher power, it is easier to assess the grade of the tumour; how closely the tumour resembles the tissue of origin (3). Histopathologists look for nuclear atypia, pleomorphism and polarity. In addition, tumour necrosis and the mitotic rate is noted – tumours with more dividing cells are described as having a high mitotic rate (3). It is also essential to note whether the tumour cells have infiltrated the basement membrane (invasive) or remain enclosed (in situ carcinoma). This classification is integral in guiding treatment: for example, transitional carcinoma of the bladder in situ requires resection as well as intravesical BCG, which differs from the treatment of invasive carcinoma.

Immunohistochemistry (IHC) is also a very important technique for pathologists in diagnostic work as well as research and clinical trials. It involves the use of antibodies for the detection of specific antigens in tissue specimens(4).

IHC can be used to confirm diagnoses, identify the primary origin of metastatic carcinoma and as a prognostic or predictive marker for therapy (4). IHC can also be helpful in predicting the prognosis of cancer through detection of gene over-expression or depletion at the protein level. These genes include proto-oncogenes, such as HER-2 in breast cancer, tumour suppressor genes (e.g. p53), tumour proliferation markers (e.g. Ki67) and growth factor receptors(4). This can, therefore, aid in the assessment of prognosis of cancer. Moreover, IHC can predict therapeutic response in cancer, such as breast, melanoma, lung and prostate carcinoma through the detection of specific receptors for growth regulating hormones on tumour cells (4). Tumours expressing a high percentage of these receptors would respond favourably to hormone therapy, which can then potentially reduce the risk of metastasis and recurrence (4). For example, oestrogen receptor (ER) positive cancers respond well to oestrogen receptor modulators, such as tamoxifen, thus highlighting the importance of identifying such upregulated hormone receptors.

Using these details, as well as the clinical background, laboratory investigations and radiological features, the histopathologist is able to produce a pathology report. The pathology report includes information about the gross description of the tissue specimen and microscopic description. The diagnosis is made, including grade, nodal status and stage. Based on morphological features of the tumour, tissue markers and information provided from IHC, predictions can be made regarding therapeutic responses to potential therapeutic options. This report is used in multi-disciplinary team meetings (MDTs) to guide treatment and further management of the patient.

Management

Depending on the results of the pathology report, oncologists and surgeons may decide to excise the tumour, treat with adjuvant or neoadjuvant chemotherapy and/or radiotherapy, watchful waiting or palliative care.

Neoadjuvant chemotherapy (NAC) involves the use of drug treatments before surgical excision of a tumour and aims to reduce tumour size (downstage) before surgery (5). This method can be used in triple negative and HER2 negative breast cancer, as well as colorectal, lung and childhood bone malignancies. Following excision or re-biopsy of the tumour and associated lymph nodes, the histopathological changes in the post-treatment sample are assessed by histopathologists to determine the pathologic response to treatment (5). This includes assessment of histological architecture, nuclear features, mitosis, tumour size and extent (6). Tumour cellularity is a very representative factor of assessing response to NAC (6). These changes are important predictors for prognosis and are being increasingly used to determine the most appropriate postoperative chemotherapy regimen (5).

Mohs micrographic surgery is a tissue-sparing method of skin cancer removal and heavily relies on histopathologists during its procedure (7). It is used for the treatment of many skin cancers, most notably basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). Mohs is appropriate for use in cancers with a high risk of recurrence and in order to conserve tissue, especially for cancers in the head and neck (7). Surgery involves removing a thin margin of tissue around the debulked tumour which is analysed under the microscope by a histopathologist; if a section of residual tumour is identified, the margin on the patient's body corresponding to the location of the residual tumour is precisely removed (7). This process is repeated until no further tumour is found, allowing for complete tumour removal and sparing of healthy tissue. This procedure has excellent 5-year cure rates – 99% for primary BCC, 92-99% for primary SCC (7). This procedure requires teamwork between the surgeon, laboratory technicians and pathologists in order to provide the best patient care.

Following excision of the tumour and associated lymph nodes (if applicable), histopathologists once again assess the gross and histological features and a final pathology report is produced. Data from pathology reports is used in cancer registry information and statistics. Any subsequent biopsies (e.g. to assess response to adjuvant therapy or cancer recurrences) are also analysed by histopathologists.

Conclusion

While histopathologists are not in direct contact with patients, their contributions to cancer diagnosis and management are quintessential. They contribute to each stage of the patient's journey and are at the forefront of cancer analysis, assessment of tumour response and proposal of treatments. The delivery of patient focused, individualise patient cancer care depends on high quality pathology services, provided by experienced histopathologists.

The Immune System and Depression: *Could there be a link?*

Written by Aishwarya Shah, University College London

Introduction

Although it is a leading cause of morbidity worldwide, one may not initially anticipate a relationship between the immune system and depression. However, with evidence from new studies suggesting inflammation could be responsible, the opportunity to investigate this cannot be missed.

Existing research

A study conducted in Canada found that when rats were induced with an inflammatory substance (2,4,6-trinitrobenzenesulfonic acid) in the gut to induce peripheral inflammation, there was a significantly greater proportion of activated microglia (1) in the CNS, known to release neurotoxic factors like cytotoxic cytokines, which then cause damage to neighbouring neurones (1)(2).

Moreover, the likelihood of osteoarthritis patients suffering from depression is 2-3 times more likely than their age-matched controls. One study, that included data from five double-blind, placebo-controlled, multicentre, randomised trials of just under 1500 patients with osteoarthritis, the subjects were screened for Major Depressive Disorder, using the Standard Patient Health Questionnaire-9 (PHQ-9). For treatment, they were divided into three groups: ibuprofen/naproxen (non-selective COX inhibitors), celecoxib or placebo. Interestingly, over six weeks of treatment, a decrease in depressive symptoms in patients with osteoarthritis was seen in the ibuprofen/naproxen and celecoxib groups (3).

Theories

The endothelial cells lining the brain's blood vessels normally have tight gaps between them and therefore only enable the smallest of molecules to enter the brain. By this rule, no inflammatory cytokines can pass this 'barrier'. However, the Blood-Brain Barrier (BBB) has been found to be more vulnerable and 'leaky' when there is increased inflammation, with increased sensitivity to inflammatory changes in some brain regions (4).

The first suggested pathway of how pro-inflammatory cytokines could enter the brain is through these 'leaky' gaps is described as the "humoral" pathway (5). In the humoral pathway, circulating pathogen associated molecular patterns

(PAMPs) from the microbes reach the circumventricular organs of the brain, as well as the choroid plexus. Circumventricular organs have highly permeable capillaries, allowing for the movement of cytokines across them without affecting the BBB (7). Here, there are macrophage-like cells which express a Toll-like receptor (TLR) that binds to the PAMP, resulting in the secretion of pro-inflammatory cytokines. It is suspected that the cytokines move from outside the BBB in the circumventricular organs, to inside the brain by volume diffusion – Figure 1 (6)(8).

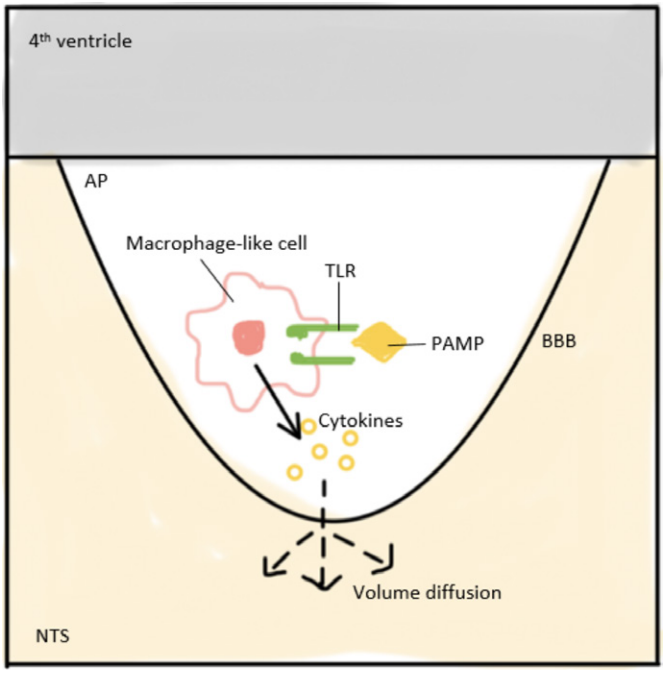


Figure 1. Diagram of volume diffusion in the brain.

The second suggested pathway is called the “neural” pathway. There are afferent nerves conducting in the direction towards the brain. Specific pro-inflammatory cytokines may bind to the cytokine receptors on these nerves, then conducting an electrical signal towards the brain (6).

Another speculated route is the "cellular route". Microglia would release chemokines to attract cells like T lymphocytes and monocytes from the periphery by chemotaxis. This, in conjunction with the involvement of adhesion molecules, would allow cytokines to enter the brain (5)(8).

The presence of pro-inflammatory cytokines in the CNS can disrupt cofactor tetrahydrobiopterin (BH4), involved in serotonin production. Certain enzymes require an attached cofactor to work, so a reduction in BH4 would negatively impact serotonin biosynthesis (5)(8). If less serotonin is made, less serotonin will be released, reducing its positive (and anti-depressant) effects. For example, an increase in IL-6 (an inflammatory cytokine) is associated with a decrease of BH4 in the cerebrospinal fluid.

Generally, a large majority of ingested tryptophan (serotonin precursor) is degraded in the liver via the kynurenine pathway, shown in Figure 2 (below), whilst the remainder is involved in serotonin-synthesis (6).

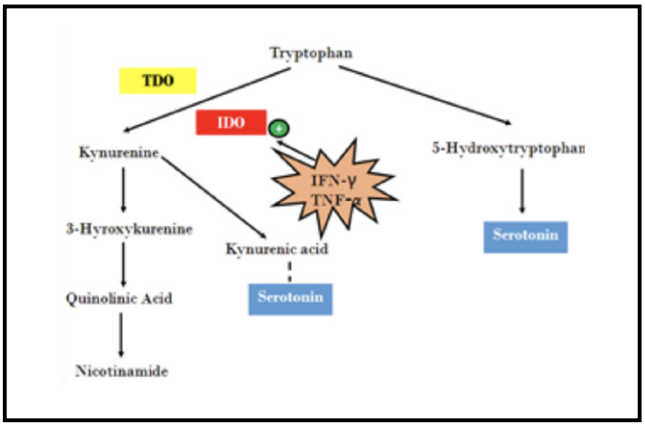


Figure 2. Tryptophan pathways

Tryptophan oxidation is normally catalysed by tryptophan dioxygenase (TDO). Alternatively, tryptophan oxidation can occur outside the liver, catalysed by indoleamine 2,3 dioxygenase (IDO). The extrahepatic pathway is normally insignificant but pro-inflammatory cytokines can highly induce IDO (6).

The 3-Hydroxykynurenine formed in the kynurenine pathway generates free radical species that could cause lipid peroxidation in addition to oxidative stress (9). Effects of oxidative stress could result in the cell membrane starting to lose integrity. Additionally, if the free radicals are charged, they could affect conductivity of the nerve cells. This could damage neurons which would ultimately affect serotonin release. Shifts in the balance of the products formed could underlie inflammation-associated depressive disorders (6).

Future Prospects

Despite limited studies and therefore reliability, the necessity of new depression treatments is urgent. Traditional treatments may not be effective for a large proportion of depression-sufferers. The severely depressed are vulnerable when using SSRIs because initial usage side effects can enhance psychomotor activities, possibly leading to completed suicide.

Mounting evidence from recent studies suggest that cytokines produced during inflammation by the immune system could be playing a fundamental role in the development of depression. Other plausible theories for depression-development exist but even then, inflammation is often a suspected contributing factor so has a crucial role in these cases as well. Medication that builds on this allegedly causational relationship can result in breakthroughs for treatment meaning inflammation can play a crucial role here too. With more research and evidence, the potential for breakthroughs in detection and treatment of depression, using inflammatory biomarkers and manipulating the immune system, could be near.

Crohn's vs Ulcerative Colitis: Histology and Treatment

Written by Meghna Tharkar, University of Birmingham

Epidemiology

Crohn's Disease (CD) and Ulcerative Colitis (UC) are two particularly prevalent conditions in the UK. Whilst 115,000 patients in the UK have a confirmed diagnosis of Crohn's disease (2), the prevalence of UC stands at 146,000 (1) with an annual incidence of dysplasia or cancer between 3.7% and 5.7% (1).

Histological differences and signs & symptoms

Patients with UC and CD display similar epidemiological and clinical characteristics, such as a young median age of diagnosis. However, there are distinct histological differences and discrepancies on presentation that aid diagnosis (Table 1). The clinical presentation of IBD can be atypical and in the early progression of disease, biopsies are fundamental in differentiating between both conditions (3). A major distinguishing factor between both IBD conditions is that CD originates in the terminal ileum whereas UC originates in the rectum. In CD, there is segmental mucosal disease worse proximally with variable rectal involvement. Patients frequently present with granulomas, transmural lymphoid aggregates and nerve fibre hyperplasia in the submucosa (3). Crucially crypt abscesses and granulomas are also only present in CD (5). By contrast, UC shows a contiguous pattern of progression limited to the submucosa or mucosa, which is worse distally. UC biopsies also illustrate crypt atrophy, cryptitis and mucin depletion in contrast to a high prevalence of granulomas, present in 21 to 37% of endoscopic biopsies (6), and focal cryptitis which favour CD over UC (3).

It is crucial that an accurate diagnosis is made before determining a treatment plan. Both UC and CD have distinctly different treatment pathways. The complications of both forms of IBD are also distinctly different. Whilst patients with CD can develop fistulas and abscesses, UC patients tend to develop toxic mega colon and anaemia through hemorrhages.

Treatment strategies

Steroids are the first line short term treatment for both UC and Crohn's disease and play an important role in acute exacerbations. The most commonly prescribed steroids for IBD include hydrocortisone and prednisolone. However, adverse effects of these include hypertension, hyperglycaemia and immunosuppression (8). Since CD patients can develop abscesses and fistulas, antibiotics are also recommended. CD also reduces vitamin absorption and hence enteral nutrition plays a key role in treatment. In mild disease patients with both diseases are also given oral aminosalicylates which counteract inflammation.

Combination therapy increases effectiveness of treatment. As disease severity increases from moderate to severe to refractory, steroid dosage increases. In the most severe Crohn's cases, patients are administered IV infliximab and oral azathioprine or mercaptopurine (7). Infliximab is contraindicated in patients with TB and hepatitis B due to its immunosuppressive properties. A select few patients with CD are also prescribed cyclosporine in acute exacerbations, although this has immunosuppressive properties and can cause tremor (9). It is administered for 7 days IV. A higher proportion of patients with UC undergo colectomies due to a number of patients showing high grade dysplasia. Notably, whilst small bowel resection via ileostomy and ileoanal pouches improve outcomes in CD, colectomies are a preferred route for UC patients since inflammation is diffuse (8). Neither disease is curable, however, accurate diagnosis microscopically and endoscopically can impact the pathway for treatment and management.

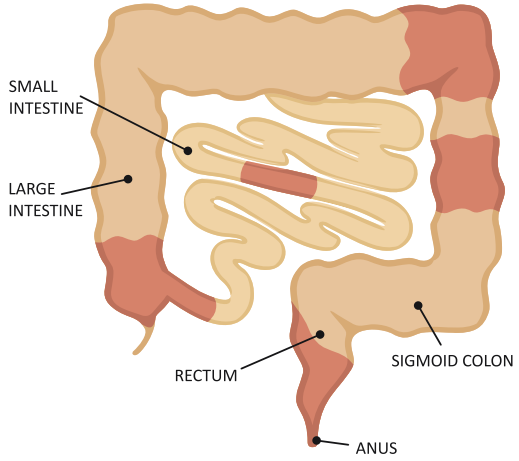
Table 1. Summary of the differences in presentation, histologic appearance and treatment of Ulcerative Colitis and Crohn's Disease

	Ulcerative Colitis	Crohn's disease
Presentation	Most prevalent in rectum. Sudden onset Diarrhea, blood and mucus in stool, tenesmus Peak age of incidence: 15 to 25 yr and 55 to 65 year	Mouth to anus, most prevalent in terminal ileum. Insidious onset Perianal injuries, fistulas common, abdominal cramping, abdominal mass, weight loss, fever Peak age of incidence: 15 to 40 years
Histological appearance	Continuous Mucosal and submucosal inflammation crypt atrophy cryptitis mucin depletion (residual mucosal tissue deposition)	Skip lesions Granulomas Transmural lymphoid aggregates Nerve fibre hyperplasia in submucosa Crypt abscesses Strictures Linear ulcerations
Treatment	Steroids (first line, short term): hydrocortisone and prednisolone Infliximab* (anti TNF alpha) Aminosalicylates e.g. mesalamine (anti-inflammatory and immunosuppressive)	Steroids (first line, short term): hydrocortisone and prednisolone Antibiotics Enteral nutrition Aminosalicylates eg mesalamine (anti-inflammatory and immunosuppressive) Infliximab Oral azathioprine** (immunosuppression: inhibition of purine synthesis) Mercaptopurine*** (antimetabolite chemotherapy: inhibition of purine synthesis) (also treats CML and AML) Cyclosporine**** (acute) (immunosuppression inhibits IL2 and T cell activation)

*contraindicated in patients with TB and hepatitis B
**contraindicated in patients with anaemia, pancreatitis, malignant lymphoma, clotting abnormalities and hepatic vein thrombosis (Budd Chiari syndrome)
***associated with hepatitis
****associated with infection, cancer, malignancy, high cholesterol, low serum magnesium, hyperkalaemia, pseudotumour cerebri and hepatitis. Do not use with NSAIDS, antibiotics and other immunosuppressants

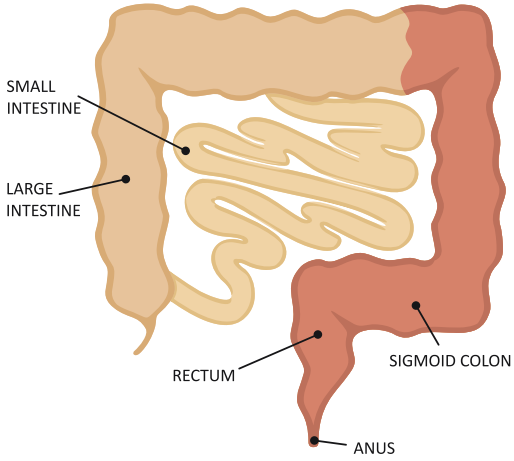
CROHN'S DISEASE

PATCHY INFLAMMATION THROUGHOUT SMALLAND LARGE BOWEL



ULCERATIVE COLITIS

CONTINUOUS AND UNIFORM INFLAMMATIONIN THE LARGE BOWEL



Recent treatment advances

JAK inhibitors

Treatment for UC and CD has improved significantly due to recent research. This is a promising sign since there is currently no cure for CD. JAK1 and microbiome targeting are two significant developments that have contributed to improved treatment outcomes. AZD4205 is a JAK1 inhibitor that binds competitively to the ATP binding site and therefore lowers cell inflammation (10). Research indicates that JAK inhibitors should be used as individual therapies and steroids stopped shortly after starting the medication. Since these medications act as immunosuppressants, it is crucial that patients are vaccinated against shingles and their TB status is identified prior to treatment (11).

The microbiome diet

The microbiome diet also has shown some signs in improvement for UC and CD patients. A trial indicated that 63.1% patients showed a decrease in disease severity over 8 weeks (10). It has also been suggested that diets high in polyunsaturated fatty acids were positively correlated with increased incidence of UC and colitis, whilst diets high in fibre lowers the risk of IBD (12). This realisation is important in future prevention of IBD and highlights the many different ways the gut microbiome impacts one's health. Patients have reported improved health with fermented products such as kombucha and oily fish, a source of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) fatty acids which are correlated with reduced inflammation. The suggested role of probiotics and prebiotics in IBD treatment is also an area of ongoing research.

Colectomy

A particularly interesting development is the potential for a reduction in UC patients requiring colectomy surgery. Data indicates that 14.7% patients have shown a reduction in colectomy rates within one year of hospitalisation of UC diagnosis (10). Colectomy plays a large role in UC patient rehabilitation due to the significant risk of colorectal cancer. This shows promise and indicates that recent biologics advancement has translated to clinical success.

Potential treatment strategies in the future

Sphingolipids

Sphingolipids are key components of the plasma membrane that protect against mechanical and chemical irritation. However, pathologically, sphingolipids ease the movement of inflammatory cells along the colon or rectum. Sphingolipids are degraded endogenously to a bioactive form Sphingophene-1-phosphate (S1P). This bioactive lipid activates G protein coupled receptors, along w with STAT3 and Nuclear Factor Kappa B. These are key transcription factors that initiate inflammation and carcinogenesis. (14). Under normal circumstances, S1P is degraded via the upregulation of SPL (SPL dominance) and the downregulation of SK1 (14). However, in UC, SK1 is upregulated and SPL is downregulated so SK1 persists (14). So biological agents targeting these biological agents may play a crucial role in lowering UC rates and reducing colorectal cancer rates derived from UC (14). Clinical trials are currently ongoing to consider the role of modified biological agents such as ozanimod in UC (13). The clinical trials are currently in Phase 3 and have indicated increased rates of clinical remission. (13). Crucially, sphingolipids derived from plant food sources, sphingodienes, are not converted to S1P (14). Research is currently in early stages (in mouse models) AND indicates that plant sphingolipid sources may display anti-inflammatory and chemo preventative roles, lowering S1P levels but increasing PTEN levels (localized to the colon). Future research will consider the role of sphingodienes in the gut mucosa and microbiome (14).

Biological agents

Research is also currently being undertaken into the potential role of biological agents in UC and CD. The main interleukins being targeted are IL12 and IL23. Ustekinumab and briakinumab target both interleukins whilst brazikumab, risankizumab, and mirikizumab target specific interleukins respectively (15). Areas to consider in the future are strategies for patient selection, treatment combinations and additional therapies, such as JAK inhibition (15). Furthermore, research will be undertaken into the side effects of emerging biological agents such as biological side effects, nausea and vomiting, and opportunistic infections. Recent research also indicates that ustekinumab may interfere in neurological pathways (16).

Finding a cure

Currently as it stands, there is no cure for Crohn's Disease or Ulcerative Colitis. However, emerging treatments such as biological agents, JAK inhibitors, diet and sphingolipids may hold great promise for the future.

Student Opinion: The Hygiene Hypothesis: Friend Or Foe?

Written by Deep Desai, University of Birmingham

The hygiene hypothesis was devised from a paper written in 1989 by Dr Strachan, an epidemiologist who found that developing atopic disease was inversely linked to family size, that infants with multiple siblings were associated with being less likely to develop atopic disorders; based on the assumption that having more siblings led to having more childhood infections, Dr Strachan suggested that childhood infections early in life reduced the likelihood of developing allergic disease (1-3).

The hygiene hypothesis stipulates that inadequate exposure to a wide variety of microorganisms and germs in the early periods of our life leads to an increased rate of future allergic disease, such as asthma and hay fever (4). This is because early exposure to a wide variety of microorganisms and germs pushes our immune system towards a Th1 phenotype, which is response for fighting against harmful microorganisms, whereas without this early exposure, our immune system is pushed towards a Th2 phenotype, which is responsible for allergy, thereby leading to future allergic disease (5).

T lymphocytes can be split into CD4 and CD8 cells (6). CD4 T lymphocytes include T helper cells, Th1 and Th2 T lymphocytes (6). CD4 T lymphocytes are known to be excellent cytokine producers, and we call the cytokines that Th1 and Th2 T lymphocytes produce Th1-type cytokines and Th2-type cytokines respectively (6). Th1-type cytokines are proinflammatory (6). On the other hand, the Th2-type cytokines, which include IL4, IL5, and IL13, are linked with promoting two parts of the immune system associated with allergy such as IgE eosinophil action in atopy (6).

It is evident that we are currently washing our hands much more frequently, interacting with fewer people, and exposing ourselves to fewer novel environments, in comparison to before the COVID-19 pandemic. The frequent washing of hands kills microorganisms and interacting with fewer people and environments reduces our exposure to a wide variety of new microorganisms and germs. Therefore, these three activities imply that our current neonates and infants are being exposed to fewer germs and microorganisms than they would have done if it were not for COVID-19. According to the hygiene hypothesis, these infants and neonates may have greater rates of future allergic disease, such as asthma and hay fever, than they would have otherwise done.

The motif behind this article is not to suggest that our current way of living is wrong, nor is it to suggest that we should be increasing our current infant's and neonate's exposure to microorganisms and germs. The idea behind this article is to suggest that if the hygiene hypothesis is correct- it is a hypothesis after all- it does seem that our current generation of infants and neonates may have higher rates of allergic disease in the future. Perhaps future research will tell us if what is being suggested in this article is indeed true.

To conclude, there are several other ways in which COVID-19 and the hygiene hypothesis have been linked. In a very recent paper by Sehrawat et al. (7), it is hypothesised that living in lower hygienic conditions in early life, as this develops the innate immune system, contributes towards reducing the severity of COVID-19 infection. This hypothesis requires further research to validate and to identify whether aspects of the immunology of the hygiene hypothesis can be used to combat COVID-19.

Dermatopathology: A Study Guide

Written by Anisah Ali, University of Birmingham

What is Dermatopathology?

Dermatopathology is a subspecialty of pathology, studying the structural and compositional changes which occur in diseases of the skin (1). From a practical aspect, a sample of the skin can be microscopically analysed and interpreted by a dermatopathologist. To examine the histopathology of the skin, a skin biopsy can be obtained and examined.

To obtain a Diploma in Dermatopathology in the UK (Figure 1), candidates must either (2):

- Have a FRCPath in histopathology
- Have a Certificate of Competence of Training (CCT) in dermatology
- Be within a year of being eligible for the CCT in dermatology

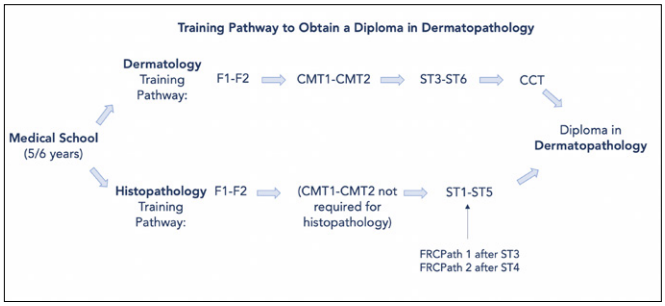


Figure 1 – pathway to a diploma in dermatopathology

The Skin

To recognise abnormal skin pathology (Table 1, 2), it is first important to be familiar with normal skin histology and anatomy. The skin can be divided into three layers. From superficial to deep, these layers are the epidermis, the dermis and the hypodermis (subcutaneous layer) (3).

Epidermis

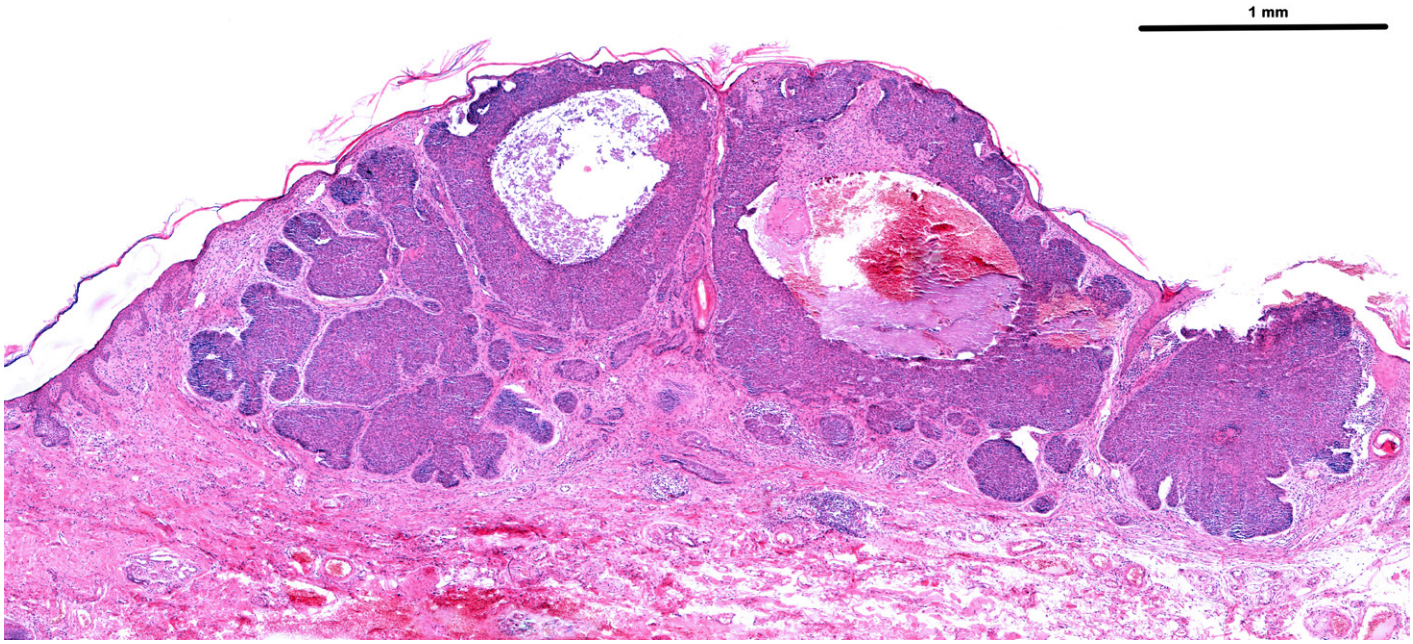
The keratinised stratified squamous epithelium of the skin. It can be divided into four cellular layers (in thin skin) and five cellular layers (in thick skin).

Dermis

The connective tissue layer is divided into two layers which are the papillary dermis (superficially) and the reticular dermis (deeper). These layers consist of collagen, elastin fibres, fibroblasts, macrophages, adipocytes and even nerves, glands and hair follicles.

Hypodermis

The hypodermis mainly consists of adipose tissue, with nerves and blood vessels.



Large basal cell carcinoma. Cords and large islands of basophilic cells compose the tumor. Inside the tumoral mass, there is necrotic and hemorrhagic material. The scale bar correspond to 1 mm.

Table 1. Common Inflammatory Pathologies of the Skin (1,4)

Condition	Pathology and Key Clinical Features	Histopathology
Dermatitis (eczema)	Most common type is atopic dermatitis, found in infancy or childhood. It is a chronic, pruritic, inflammatory disease characterised by itchy, dry and sometimes red skin.	Spongiosis is often found in acute eczema. In chronic eczema, the epidermis may thicken and acanthosis may occur.
Psoriasis	Chronic inflammatory skin disorder, occurring due to T-cell mediated autoimmunity, stimulating keratinocyte hyperproliferation and cytokine production. The most common form is chronic plaque psoriasis. Often characterised by well-circumscribed, erythematous patches with a silvery white scale. A white halo surrounding the psoriatic plaque, known as a Woronoff ring, may be seen.	Neutrophils are found in the stratum corneum and squamous cell layer. There may also be signs of hyperkeratosis and hypogranulosis.
Lichen Planus	Identified by violaceous, flat-topped, pruritic papules. One may also find Wickham's striae (fine white lines) and oral lesions.	A band-like infiltrate of lymphocytes may be seen. Other common findings are wedge-shaped hypogranulosis, a saw-tooth lower epidermis and scattered Civatte bodies and colloid bodies.
Bullous Pemphigoid	A bullous lesion without an erythematous base may be seen.	A sub epidermal blister is usually seen, with a viable roof over the new blister or a necrotic roof over an old blister.

Table 2. Cutaneous Tumours of the Skin (1,4,6)

Condition	Pathology and Key Clinical Features	Histopathology
Seborrheic Keratosis	Pigmented lesions of the epidermis. Milia (round whitish/ yellow structures) or comedo-like openings (surface invaginations) can be found. 5	Generally, signs of hyperkeratosis, papillomatosis and acanthosis. Also, basaloid keratinocytes, abundant melanin in the basal layer and sharp boundary at the border of any epidermal hyperplasia.
Basal Cell Carcinoma (BCC)	Most common form of skin cancer, classified as a malignant tumour of keratinocytes. May find a pink-white shiny area or blue-grey globules. Nodular BCC is the most common subtype.	Variability depending on the type of BCC. Usually groups of basaloid cells present, with peripheral palisading nuclei and cleft formation between the tumour nest and dermis.
Solar Keratosis (Actinic Keratosis)	Scaly, rough, hyperkeratotic patches on an erythematous background. May be tender.	Alternating columns of parakeratosis and orthokeratosis. Hyperkeratosis and/or ulceration and basal atypical keratinocytes can be found.
Intraepidermal Squamous Cell Carcinoma (SCC) /Bowen Disease (Figure 2)	SCCs often present with shallow ulcers, with a keratinous crust.	Presents similarly to acitinic keratosis (Figure 1). Hyperkeratosis and parakeratosis may be present. Generally, nests of atypical keratinocytes are seen invading the dermis.
Malignant Melanoma	An irregular pigment network with aggregated globules, asymmetrical colour/structure and a pink veil.	Proliferation of atypical melanocytes, which invade upwards through the epidermis and downwards into the dermis.

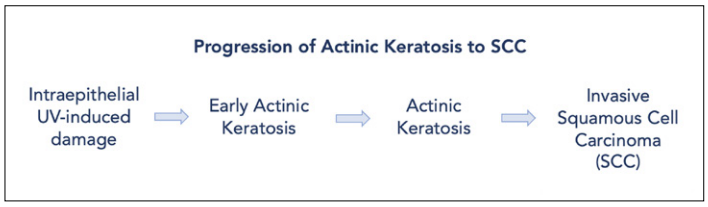


Figure 2 – Progression of actinic keratosis to squamous cell carcinoma

Clinical Pathology Key Words:

- Bullous – characterised by bullae, which are large blisters
- Erythema – red skin as a result of an increased blood supply
- Nodule – elevated, solid, palpable lesion > 1cm
- Papule – elevated, solid, palpable lesion less than or equal to 1cm in diameter
- Plaque – well-circumscribed, palpable lesion > 1cm in diameter, generally elevated
- Pruritic – related to itching
- Violaceous – violet/purple in colour

Histopathology Key Words:

- Acanthosis – thickening of the epidermis and elongation of the rete ridges
- Basaloid – resembling epidermal basal cells
- Civatte bodies – spherical bodies formed by necrosis of individual basal cells
- Hyperkeratosis – thickening of the stratum corneum
- Hypogranulosis – decreased thickening of the stratum granulosum
- Papillomatosis – irregular, undulating, folding of the epidermal surface
- Parakeratosis – keratinised cells of the skin surface retain their nuclei leading to an abnormal stratum corneum
- Rete ridges – upward projection of dermis between epidermal rete pegs
- Spongiosis – intercellular swelling of the epidermis

Dermatopathology of Covid-19:

A Pictorial Guide to Clinical And Histopathological Features of Covid-19 on the Skin

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Yasmin Kamel, University of Buckingham

Figure 1. Urticarial rash

Urticarial Pattern

Clinical features

- Itching urticarial rash predominantly involving the trunk and limbs

Histopathological features

- Vacuolar interface dermatitis with superficial perivascular lymphocytic infiltrate

Differential diagnoses

- Ordinary urticaria
- Other viral exanthems

Treatment options

- Non-sedative anti-histamine
- In severe cases low dose systemic corticosteroids may be considered

COVID-19 prognosis correlation

- Presence of rash is not correlated with COVID-19 prognosis (5)

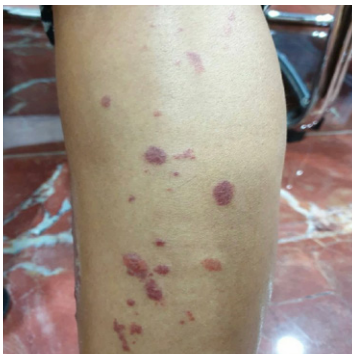

Figure 2. Erythematous maculopapular rash

Erythematous Maculopapular pattern

Clinical features

- Symmetrical generalised maculopapular eruption on the trunk and proximal extremities
- Purpuric lesions may coexist

Histopathological features

- Superficial perivascular lymphocytic infiltrate
- Infiltration of neutrophils may be seen

Differential diagnoses

- Drug eruptions
- Other viral infections

Treatment options

- In mild disease topical corticosteroids
- In severe disease systemic corticosteroids

COVID-19 prognosis correlation

- Presence of rash is not correlated with COVID-19 prognosis (5)

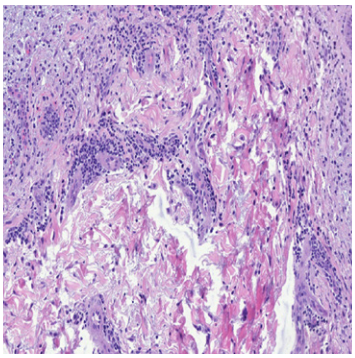

Figure 3. Histopathology of Papulovesicular exanthema (8)

Papulovesicular Exanthema

Clinical features

- Generalised Polymorphic pattern of small papules, vesicles and pustules
- Localised pattern of papulovesicular lesions involving the upper trunk

Histopathological features

- Notable acanthyolysis and dyskeratosis associated with unilocular intraepidermal vesicles
- Vesicles in a suprabasal location

Differential diagnoses

- Varicella
- Peleva

Treatment options

- Wait and see
- Symptomatic relief - anti histamine, topical calamine lotion

COVID-19 prognosis correlation:

- Presence of rash is not correlated with COVID-19 prognosis (5)

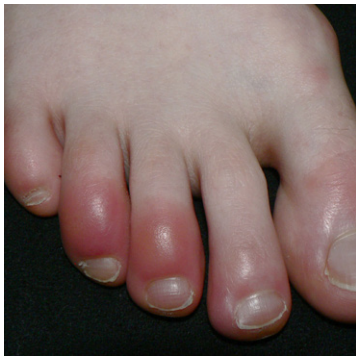

Figure 4. Chilblains

Chilblain like Acral Pattern

Clinical features:

- Erythema and inflammation on acral areas

Histopathological features

- Periadnexal dermal lymphocytic infiltrates
- Perivascular infiltrates

Differential diagnoses

- Dermatomyositis
- Cholesterol emboli

Treatment options

- Wait and see
- Symptomatic relief - avoidance of cold, protection of toes from trauma and cold

COVID-19 prognosis correlation:

- Presence of rash is correlated with worse COVID-19 prognosis (5)

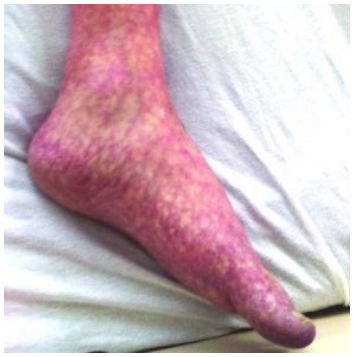

Figure 5. Livedo reticularis secondary to obscure severe infrarenal aortoiliac stenosis with severe transient lactic acidosis.

Livedo Reticularis like Pattern

Clinical features

- Net like erythema on extremities
- May be temperature dependent

Histopathological features

- Slight endotheliitis with usually no necrotic features
- Pauci-inflammatory micro thrombotic vasculopathy

Differential diagnoses

- Lupus erythematosus
- Protein C/S deficiency

Treatment options

- Wait and see
- Avoid extremes of temperature

COVID-19 prognosis correlation

- Presence of rash is correlated with worse COVID-19 prognosis (5)

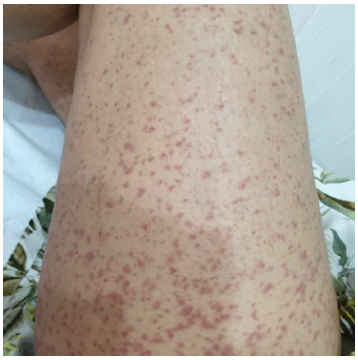

Figure 6. Purpuric rash

Purpuric Pattern

Clinical features

- Generalised non blanching eruption

Histopathological features

- Severe perivascular infiltrate
- Erythrocytic extravasation
- Hemosiderin deposition causing variable pigmentation

Differential diagnoses

- Rickettsial infection (Rocky Mountain spotted fever)
- Thrombocytopaenia

Treatment options

- In mild disease topical corticosteroids
- In severe disease systemic corticosteroids

COVID-19 prognosis correlation

- Presence of rash is not correlated with COVID-19 prognosis (5)

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