THE NORTHERN HOSPITAL

VESICULOBULLOUS (BLISTERING) SKIN DISEASE

"Louis XV", (1710-1774), oil on canvas, 1748, Maurice Quentin de La Tour.

April Thursday 28th

King's illness

April Friday 29th

In the morning - the smallpox is diagnosed.

May 7th

Last rights of the King at 6 in the morning

May 10th

Death of the King at 2 in the afternoon

Diary entries of the Dauphin, April-May 1774.

He was lying on his bed camp in the middle of the room, all curtains wide open, brilliantly lit by a quantity of candles held by the priests, who were wearing their surplices and kneeling around the bed....His face, swollen by the scabs, was the colour of bronze....His chest was immobile, his mouth open, but his face was not misshapen and showed no agitation; in a word, it looked like a Moor's, a negro head, dark and swollen...

The Bishop of Senlis, standing recited the last prayers....all the other people present also stood and looked horrified....there was, overall, more etiquette than feeling...

On May 10....he remained conscious till noon and showed, as before, the greatest patience, firmness, quiet, and acceptance. At three - fifteen he expired.

Journal of the Duke de Croy, 1718-1784.

Smallpox was always present, filling the churchyard with corpses, tormenting with constant fear all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of the betrothed maiden objects of horror to the lover….

TB Macaulay, The History of England from the Accession of James II. Philadelphia: Claxton, Remsen & Hafielfinger; 1800.

Since antiquity, humanity has been scourged with many devastating infectious diseases, including malaria, tuberculosis, typhoid, typhus, and the plague - but none have been more continuously relentless and feared than the smallpox. It did not discriminate between the lowliest of peasants or the greatest of Kings. Completely healthy individuals could be dead within two weeks of contracting the disease. Many times it altered the course of human history, in some cases bringing down empires, including the Aztec and the Inca. In the 21st century smallpox has finally been eradicated from the Earth - and

this must surely rank as one of the greatest triumphs of Medicine. The turning point in the battle against this ancient enemy, came with the brilliant work of Edward Jenner at the end of the Eighteenth century. Variable success had been achieved with "variolation" a crude form of immunization, but it was Jenner who developed the definitive modern technique of vaccination. He noted that milkmaids who contracted cowpox from contact with cow udders were immune to smallpox; in the words of Barquet and Domingo "he listened to their folk wisdom, and raised it to the status of scientific fact".

Though Jenner is credited with the discovery of smallpox vaccination, he was building on the previous work of variolation. This crude form of vaccination was brilliantly promoted, not by any doctor, but by an extremely intelligent aristocratic woman by the name of Lady Mary Wortley Montague.

Barquet and Domingo tell her story:

"The English aristocrat Lady Mary Wortley Montague was responsible for the introduction of variolation into England. She had an episode of smallpox in 1715 that disfigured her beautiful face, and her 20 year old brother had died of the illness 18 months earlier. In 1717, Lady Montague's husband, Edward Wortley Montague, was appointed Ambassador to the Sublime Porte; the family left for Istanbul on 15 March. Two weeks after her arrival. Lady Montague wrote to her friend Sarah Chiswell (who died of smallpox 9 years later) and described the method of variolation used at the Ottoman court. She called it "ingrafting"; it was a procedure done by old women, who made four or five scratches or a slight puncture on the arm and introduced material taken from smallpox pustules from patients who had mild cases of the disease. Lady Montague was so determined to prevent the ravages of smallpox and so impressed by the Turkish method that she ordered the Embassy surgeon, Charles Maitland, to inoculate her 5-year-old son in March 1718.

On returning to London in April 1721, she had Maitland inoculate her 4 year old daughter in the presence of the physicians of the court. Among these physicians was Sir Hans Sloane, President of the Royal Society and the king's physician. This was the first professional variolation performed in England. Word of these practices spread and reached the Princess of Wales and other members of the Royal Family. Charles Maitland was granted royal license to perform a trial of variolation on six prisoners at Newgate on 9 August 1721; these prisoners were promised a full pardon if they submitted to the so-called Royal Experiment. The trial was observed by the court physicians and 25 members of the Royal Society and the College of Physicians. All of the prisoners survived and were released. One was exposed to two children with the illness and proved to be immune. Maitland later variolated six charity children in London and successfully treated the two daughters of the Princess of Wales on 17 April 1722. Not surprisingly, the procedure gained general acceptance after this last success. Two to three percent of variolated persons died of smallpox; became the source of a new epidemic; or developed other illnesses from the lymph of the donor, such as tuberculosis or syphilis. Nonetheless, case-fatality rates were 10 times lower than those associated with naturally occurring smallpox, and artificial inoculation was widely practiced until Jenner's discovery; indeed, Jenner himself was variolated at 8 years of age.

The primary side effect of the procedure was the appearance of smallpox itself; however, in 1722, in one of the first applications of statistics to a medical and social problem, James Jurin observed that the smallpox-associated ease fatality rate was 1:14 in non-inoculated children and 1:91 in inoculated children. With new improvements that reduced the likelihood of serious infection, the technique became widespread in England and reached towns and rural communities by the 1740s. In 1745, the London Smallpox and Inoculation Hospital was founded; this center was dedicated exclusively to the treatment and prevention of smallpox".

In 21st century medical practice we frequently face the difficult dilemma of assessing patients who present with vesiculobullous eruptions. Thanks to the brilliant work of Lady Mary Wortley Montague and Edward Jenner and many others that followed them, we now no longer need include amoung our differential diagnoses, one of the most ancient and most terrible scourges of humanity - smallpox.

Left: Mary Wortley Montagu, oil on canvas, c.1716, Charles Jervas, National Gallery of Ireland. Right: Edward Jenner, oil on canvas, c.1803 James Northcote, National Portrait Gallery, London.

VESICULOBULLOUS (BLISTERING) SKIN DISEASE

Introduction

Vesiculobullous (or Blistering) disorders constitute a diverse group of conditions in which fluid accumulates in the skin as a result of damage to the epidermis, epidermo-dermal junction or the upper dermis.

Blisters most commonly form in response to a specific injury such as a burn, insect bite or bacterial or viral infection (see list below).

Infection, Drug reaction and Autoimmune are the most common groups of causes.

Many vesicular/ bullous reactions will not have a clear diagnosis after history and examination, and in these situations a punch type biopsy will now usually be done.

For widespread erythrodermic type reactions, important management considerations, irrespective of an exact diagnosis, will include, prevention of hypothermia, fluid resuscitation, and prevention of secondary bacterial infection.

Pathology

The causes of vesiculobullous skin lesions include:

Most commonly:

1. Blistering skin infections:
    - Chickenpox (varicella)
    - Herpes simplex
        - ♥ Including eczema herpeticum
    - Herpes zoster (shingles)
    - Impetigo
    - Hand foot & mouth disease
    - Staphylococcal scalded skin syndrome
2. Envenomation:
    - Insect bites
    - Spider bites

3. Environmental injury:
    - Cold Injury
    - Thermal injury
    - Chemical injury
4. Dermatitis:
    - Plant dermatitis
    - Contact dermatitis
5. Drug reactions:
    - Generalized or Fixed bullous drug eruption.

Less commonly:

6. Primary or autoimmune blistering skin diseases:
    - Eczematous conditions
        - ♥ Dyshidrosis (pompholyx)
    - Bullous pemphigoid (and variants)
    - Pemphigus (and variants)
    - Erythema multiforme/ Toxic epidermal necrolysis/ Stevens - Johnson Syndrome
    - Dermatitis herpetiformis
        - ♥ Dermatitis herpetiformis is associated with gluten-sensitive enteropathy in the majority of cases (at least 85%) although this may be asymptomatic.
    - Sweet's syndrome
    - Linear IgA disease
    - Pyoderma gangrenosum

Rarely:

7. Metabolic diseases:

- Porphyria cutanea tarda

8. Genetic diseases:

    - Epidermolysis bullosa:

      Epidermolysis bullosa refers to a group of rare inherited disorders in which there are mutations in specific keratin proteins (EB simplex), hemidesmosomes (junctional EB), anchoring filaments or type VII collagen (dystrophic EB).

      Minor trauma results in blisters and erosions, the split site and severity depending on the specific defect.

Clinical assessment

Important points of history:

1. Contact with any noxious chemicals or plants
2. Trauma or environmental injury
3. Medications
4. Co-morbidities/ past history
5. **Any associated systemic symptoms**
6. Any **definite** insect/animal bites.

Important points of examination:

1. Vital signs

    - Fever, suggests an infective cause

2. Assessment of the site of splitting:

    Blisters are accumulations of fluid within or under the epidermis.

    Diagnosis is aided by an estimation of the site of the intercellular split as follows:

    - Subcorneal:

        ♥ Very thin roof breaks easily

        Examples: Impetigo, miliaria, SSSS

- Intra-epidermal:
  - ♥ Thin roof ruptures to leave denuded surface

    Examples: Acute eczema, varicella, herpes simplex, pemphigus
- Subepidermal:
  - ♥ Tense roof often remain intact

    Examples: Bullous pemphigoid, dermatitis herpetiformis, erythema multiforme, TEN, friction blisters

Investigations

Investigations will be guided b the degree of clinical suspicion for any given pathology, as well as for possible secondary complications:

The following may need to be considered:

Blood tests:

- FBE
- CRP
- U&Es/ glucose
- LFTs

A range of specialized blood tests may also be used to measure the amount and type of auto-antibody in autoimmune blistering diseases, and for genetic testing in inherited blistering diseases.

Microbiology

Take fluid for:

- Microscopy and culture
- PCR viral studies

Biopsy:

Many vesicular/ bullous reactions will not have a clear diagnosis after history and examination, and in these situations a punch type biopsy will now usually be done for histological examination.

In autoimmune blistering disorders, clinical patterns may be helpful, but diagnosis usually *requires* **histology** and **immunofluorescence studies.**

Immunofluorescence requires a fresh specimen in a special transport medium.

Management

Management of course will be directed to the underlying cause, in addition to the symptoms.

Infective causes are treated with antimicrobials where available and topical antiseptics

Control of immunobullous diseases can be very difficult. Maintenance therapies are usually required for years if not lifelong and are likely to result in significant complications.

For widespread erythrodermic type reactions, important management considerations, irrespective of an exact diagnosis, will include, prevention of hypothermia, fluid resuscitation, and (where the cause is not infective), prevention of secondary bacterial infection.

In general terms modalities of treatment include:

Dressings:

Modified dressings for inflammatory dermatoses can include: [2]

Occlusive dressings:

- Occlusion with an impermeable film increases absorption of a topically applied preparation and promotes rehydration by moisture retention.
- It is used especially to increase absorption of topical corticosteroids.
- It may be used where skin surfaces are thick (e.g. on the palms and soles), or where the dermatosis is hypertrophic (e.g. in nodular prurigo, hypertrophic lichen planus), or in a hypertrophic scar.
- Clean the skin and apply the topical preparation while the skin is damp.
- Cover with a waterproof dressing or plastic film wrap.
- Possible adverse effects of occlusion include maceration, folliculitis and miliaria. Occlusion will potentiate the adverse effects of topical corticosteroids, such as atrophy and telangiectasia

Wet dressings:

- Wet dressings allow greater penetration of topically applied corticosteroids by overhydration of the epidermis.

- They are useful in settling a severe or acute eruption but are generally only needed for a few days. Several different methods are used (see appendix 1 below for a commonly used method).

- They can be used 3 to 4 times a day and stopped once significant improvement occurs.

- The application of a potent topical corticosteroid over a large area with wet dressings can lead to significant systemic absorption.

- The main complications of prolonged use of wet dressings are adverse effects from systemic absorption of corticosteroid and folliculitis

Medications:

These can include:

- Systemic **steroids:**
  - ♥ Oral prednisone or pulsed IV methyl prednisolone.
- Ultrapotent topical steroids (Unsuitable for widespread disease)
- Nicotinamide
- Certain oral antibiotics:
  - ♥ Tetracyclines: doxycycline or minocycline 200mg daily
  - ♥ Dapsone, salazopyrin, erythromycin
- Immunosuppressive agents:
  - ♥ Azathioprine, methotrexate, chlorambucil, cyclosporin, tacrolimus, mycophenolate mofetil, cyclophosphamide
- Intravenous immunoglobulin (very expensive)
- Plasma exchange

Specific measures:

For some conditions there will be an appropriate specific treated, e.g. anti-viral agents or antibiotic agents.

Supportive measures:

These are given as required and may include:

- IV fluid resuscitation.
- Correction of electrolyte disturbances.
- Prevention or treatment of secondary bacterial infection.
- Protection from hypothermia

Patient Resources

The Australasian Blistering Diseases Foundation:

- http://blisters.org.au/

Appendix 1

Wet dressings technique:

1. Patient has a bath or shower or wets the affected area.

2. Patient sits or lies on plastic sheeting.

3. Apply the topical preparation.

4. Cover with wrung-out wet dressings (use wet towels, sheets, gauze bandages or pyjamas, cotton socks for feet, cotton gloves for hands and a water temperature that is comfortable for the patient).

5. Apply more warm water if necessary for warmth.

6. Remove the wet dressings after approximately 15 to 60 minutes.

7. Dry the skin.

8. Apply a moisturizer.

References

1. Blistering Skin Disease: from the New Zealand Dermatological Society:

   - dermnetnz.org/

2. Dermatology Therapeutic Guidelines, 3rd ed 2009.

Further reading:

Nicolau Barquet, Pere Domingo, "Smallpox: The Triumph over the Most Terrible of the Ministers of Death". *Ann intern Med.* 1997; 127:635-642.

Jennifer Lee Carrell: "The Speckled Monster: a Historical Tale of Battling Smallpox", Dutton, 2003.

Dr J. Hayes
November 2014