8.5.5 Mumps Epidemic parotitis 769

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8.5.5 Mumps: Epidemic parotitis 769 disease virus, is considered a tanapox virus strain). These viruses rep- licate slowly in cell culture and cause zoonotic infections in humans. Tanapox virus was isolated in the Tana valley in Kenya (1957–1962) from humans suffering from localized skin lesions typical of pox- viruses (Fig. 8.5.4.7). Probably the virus is transmitted from infected monkeys by biting insects, particularly during wet weather condi- tions. Usually it produces a solitary lesion that is preceded for a few days by a mild fever. The lesion takes 5 to 6 weeks to clear and is dis- tinguished from other poxvirus lesions by its failure to become pus- tular. This virus cannot be cultured on the chorioallantoic membrane. Yaba monkey tumour virus was discovered in Yaba, Lagos, Nigeria in 1957 as a virus causing cutaneous histiocytomas in rhesus mon- keys and can infect humans if injected subcutaneously or intrader- mally. The lesions are not neoplastic and are cleared by the immune response. Cutaneous poxviruses (Orf virus and molluscum contagiosum virus) See Chapters 8.5.27 and 8.5.28. FURTHER READING Andrei G, Snoeck R (2010). Cidofovir activity against poxvirus infec- tions. Viruses, 2, 2803–30. Damon IK (2011). Status of human monkeypox clinical disease, epi- demiology and research. Vaccine, 29 Suppl 4, D54–9. Di Giulio DB, Eckburg PB (2004). Human monkeypox: an emerging zoonosis. Lancet Infect Dis, 4, 15–25. Domi A, Moss, B (2002). Cloning the vaccinia virus genome as a bacterial artificial chromosome in Escherichia coli and recovery of infectious virus in mammalian cells. Proc Natl Acad Sci USA, 99, 12415–20. Duggan A, et al. (2016). 17th century variola virus reveals the recent evolution of smallpox. Current Biol, 26, 3407–12. Fauquet CM, et al. (eds) (2005). Virus taxonomy: eighth report of the international committee on the taxonomy of viruses. Elsevier, Amsterdam. Fenner F, et al. (1988). Smallpox and its eradication. World Health Organization, Geneva. Fenner F, Wittek R, Dumbell KR (1989). The orthopoxviruses. Academic Press Ltd, London. Hwenda L, Larsen BI (2011). The remaining smallpox stocks: the wrong debate? Lancet, 378, e7; author reply e7. Mercer AA, Schmidt A, Weber O (2007). Poxviruses. Berhäuser- Verlag, Berlin. Moss B (2007). Poxviridae: the viruses and their replication. In: Knipe DM, et al. (eds) Field's virology, 5th edition, 2, pp. 2905–46. Lippincott Williams & Wilkins, Philadelphia, PA. Moss, B (2012). Poxvirus cell entry: how many proteins does it take? Viruses, 4, 688–707. Putz M, et al. (2006). Quantification of antibody responses against multiple antigens of the two infectious forms of vaccinia virus provides

a benchmark for smallpox vaccination. Nature Med, 12, 1310–15. Williams G (2010). Angel of death: the story of smallpox. Palgrave Macmillan, Basingstoke. 8.5.5 Mumps: Epidemic parotitis B.K. Rima ESSENTIALS Mumps is an acute, systemic, highly infectious, communicable in- fection of children and young adults, caused by a paramyxovirus (with an RNA genome). Transmission is by airborne droplet spread. After an incubation period of 14 to 18 days, typical presentation is with fever, pain near the angle of the jaw, and swelling of the parotid glands. Complications include orchitis, meningitis, and encephalitis. Diagnosis is obvious clinically in cases with a con- tact history and parotitis, but serological (mumps-specific IgM and IgA) and RNA-based (RT-PCR) tests are used when this is not the case (e.g. the patient presenting with meningitis). Treatment is symptomatic. Prevention is by vaccination, often given as one component of a trivalent mumps/measles/rubella vaccine at 14 to 16 months of age. A follow-up vaccination is now recommended at 4–5 years of age. Introduction and historical perspective The primary clinical manifestation in mumps, swelling of the salivary glands, is so characteristic that the disease was recognized very early as different from other childhood illnesses. Hippocrates described the disease in the 5th century BC and also noted swelling of the testes (orchitis) as a common complication of mumps. In 1790, Hamilton noted the infection in the central nervous system and meninges. In 1934, mumps was shown to be a filterable virus by Johnson and Goodpasture, who also fulfilled Koch’s postulates by infecting volun- teers with virus propagated in monkeys. Since 1967, live attenuated vaccines have been licensed to control and prevent the infection. Fig. 8.5.4.7 Tanapox lesion on the leg of a Kenyan patient. Courtesy of the late P. E. C. Manson-Bahr.

770 section 8 Infectious diseases Aetiology and genetics Mumps virus (MuV) can be grown in tissue cultures of chick em- bryo, monkey kidney, and most human cells. The virus can also be cultured in the yolk sac or embryonic cavity of chick embryos. Cytopathic changes (syncytium formation and cell rounding) may be seen as early as 24 h postinfection and earlier if immunofluor- escence is used. MuV is thermolabile. It can be stored for years at –70°C, but infectivity is lost in a few days at room temperature. Treatment with ether or paraformaldehyde inactivates the virus rap- idly, but does not destroy the antigens responsible for reactivity in classical and no longer routinely performed tests such as comple- ment fixation, haemagglutination, or reactivity in the skin. MuV is an enveloped RNA virus with a genome of 15 384 nu- cleotides. Its inner core is a ribonucleoprotein complex (the nu- cleocapsid) containing the nonsegmented, negative-strand, RNA molecule encapsidated by the nucleocapsid protein (N). The nucleocapsid has the herringbone structure characteristic of paramyxoviruses (Fig. 8.5.5.1a). Attached to this are two further proteins involved in transcription and replication of the RNA genome: the phosphoprotein (P) and the large replicase protein (L). The nucleocapsid is surrounded by a lipid bilayer (Fig. 8.5.5.1a, b). On the inner leaflet is a membrane or matrix protein (M) that plays an essential role in virus budding. On the outer surface are two glycoproteins, one carrying the haemagglutinin-neuraminidase activity (HN), the other is the fusion protein (F). A complex be- tween the HN and F proteins is responsible for the fusion of the virion membrane with that of the host cell. The function of a non- structural, small hydrophobic protein (SH) is unknown; it is asso- ciated with the endoplasmic reticulum in MuV-infected cells. The SH protein sequence is hypervariable and this is used to assign MuV strains to one of 12 currently recognized genotypes. The non- structural V protein functions in combating the host’s innate im- mune response by targeting STAT 1 and STAT 3 for degradation. The gene order (Fig. 8.5.5.1c) leads to an expression gradient in which the abundance of mRNAs decreases with increasing distance to the promoter at the 3'-terminal end of the genome, so that the N mRNA is more abundant than the L mRNA. Epidemiology and pathogenesis Mumps is highly infectious.

Transmission depends on close per- sonal contact with a patient who is excreting virus in the saliva and spreading it in droplets. In the prevaccine era, the peak incidence was in the late winter or early spring, in 3–7-year cycles. Most morbidity is associated with meningitis and orchitis. Case fatality is about 2 per 1000. The incubation period lies between 14 and 18 days. In any outbreak, 30 to 40% of those infected have subclinical illness. MuV causes an infection of the upper respiratory tract that spreads to draining lymph nodes. The subsequent viraemia and infection of lymphocytes and macrophages causes spread to many organs, but because mumps is so rarely lethal, details are scant. Mumps virus can spread to most organs in the body. Lymphocytic infiltration and (b) HN RNA L P N M F (c) M N Genome 3' 5' N H SH P / V 549 224 170 375 102 436 57 582 2261 F2 F1 54 1906 3226 4481 6209 6522 15384 8428 L 391 (a) Fig. 8.5.5.1 Structure and genome organization of the mumps virus: (a) a disrupted, negatively stained, mumps virion. The viral nucleocapsid protrudes from the particle and the fringe of
viral spikes is visible (bar = 100 nm); (b) diagram of the localization of the nucleocapsid (N), phospho- (P), large (L), matrix (M), haemagglutinin-neuraminidase (HN), and fusion (F) proteins in the mumps virion; and (c) structure of the genome of mumps virus indicating the localization of the genes, the nucleotide number of their starting and stopping position, and (in boxes) the number of amino acid residues in each of the viral proteins.

8.5.5 Mumps: Epidemic parotitis 771 destruction of periductal cells lead to blockage of the ducts both in salivary glands and in the seminiferous tubules of the testes. The lymphatics in the tissues surrounding and overlying the parotid glands become obstructed, producing a gel-like oedema that may spread down over the chest wall, especially when the swelling of the salivary glands is severe. Rarely, mumps causes hydrocephalus by destruction of the lining of the aqueduct. Clinical features and diagnosis Parotitis A patient with mumps parotitis may have a fever without rigors (40– 40.5°C) as well as pain near the angle of the jaw. The face and neck become distorted with swelling. The skin over the gland is hot and flushed but there is no rash, unlike in the swelling of erysipelas. If the swelling is severe, the mouth cannot be opened for pain and tight- ness, and is dry because the flow of saliva is blocked. This lasts for 3 or 4 days. Sometimes, as one side clears, the parotid on the other side swells. When there is bilateral parotitis, clinical diagnosis is usu- ally obvious. One condition that must be excluded is bull neck diph- theria (Chapter 8.6.1), which can look very like mumps. Rarely, the submaxillary and sublingual salivary glands may also be affected. The symptoms are similar to those in parotitic mumps, but it is difficult or impossible to distinguish the swelling from other forms of submaxillary swellings, especially inflammation of various groups of lymph nodes and Ludwig’s angina. In mumps, the neck swelling is ill-defined, and the angle of the jaw is impalpable. To de- termine if cervical lymph nodes are swollen from some other cause, the pharynx must be examined carefully. The fauces must be exam- ined for signs of tonsillitis that might cause cervical adenitis. The lymph nodes in contact with the submaxillary and sublingual sal- ivary glands drain the corner of the eye, the side of the nose, the cheeks, the lips, and the floor of the mouth, all of which must be explored, before a diagnosis of submaxillary or sublingual mumps can be made. Laboratory tests are needed to confirm the diagnosis. Other alternative diagnoses need to be considered. In infectious mononucleosis, the glands stand out distinctly and the parotid is not affected. In septic parotitis there is more parotid tenderness; there may be fluctuation, and pus exudes from the orifice of Stensen’s duct. Calculus causes spasmodic pain and swelling and may be detected radiographically. Recurrent parotitis and Mikulicz’s syndrome are unlikely to be confused with mumps except in the earliest stages, nor are uveoparotid fever and tumours of the gland, as they are chronic conditions. Orchitis Orchitis may occur 4 or 5 days after the onset of parotitis. Quite often it occurs without preceding parotitis. It is an acute condition, with chills,

sweats, headache, and backache, and a swinging temperature as well as severe local testicular pain and tenderness. The scrotum is swollen and oedematous, and the testicles are impalpable. Usually, only one testicle is affected but sometimes both: the second testicle may become affected just as the swelling of the first is subsiding. The illness lasts 3 or 4 days before the swelling begins to subside. Orchitis is unusual before the age of puberty, though it has occurred in young boys and even in infants. In adolescent and young males it develops in 1:5 cases. Some degree of atrophy of the testicle occurs in at least one-third of patients with orchitis. Azoospermia after mumps is rare and only temporary. The fear of sterility after mumps orchitis has been exaggerated and one can reassure the patient. Orchitis when it occurs without parotitis is difficult to distinguish from gonococcal epididymo-orchitis, unless there has been contact with mumps. The rare case of orchitis in infancy may resemble torsion of the testis and perhaps it is safer to operate than risk a serious misdiagnosis. Meningitis and encephalitis MuV frequently invades the nervous system: changes in the elec- troencephalogram and increased levels of protein and lymphocyte levels in the cerebrospinal fluid can be shown in at least half the pa- tients. However, in most cases, neurological symptoms or signs are absent. Mumps virus was one of the most common known causes of lymphocytic meningitis. This may develop a few days after the start of parotitis, but almost as often it occurs in the absence of parotitis. Occasionally, the patient develops transient paralysis of limbs re- sulting in the occurrence of quadriplegia or single nerve paralysis in some patients. Polyneuritis, neuritis of the trigeminal or facial nerve, and retrobulbar optic neuritis have been described in mumps but all are rare. The meningitis is usually mild and self-limiting. Mumps encephalitis is a different entity; cerebrospinal fluid is normal and contains no virus. The outlook is different. The patient is confused and may lapse into coma and remain comatose for days, weeks, or months. Almost 2% of the encephalitis cases are fatal. At autopsy there is perivascular demyelination as in other forms of postinfectious encephalitis (Chapter 24.11.2). Other complications Deafness is reported in up to 0.3% of the cases, but it is rarely per- manent and often unilateral. Women sometimes complain of ovarian pain during an attack of mumps, but it is rarely as severe as in men with orchitis. There is no evidence that it affects fertility. Mastitis occurs in 15% of the cases, both in men and women, but it is usually mild and fleeting. Mild upper abdominal pain in about 50% of the cases may be related to viral changes in the pancreas. The amount of amylase in duodenal fluid may be less than normal. This is probably caused by a blockage of the ducts in the pancreas. Although there are anecdotal reports of diabetes occurring after an attack of mumps, there is no virological or immunological evidence for a direct link though the virus is known to be able to infect the pancreatic islet B cells. Mumps in the fetus and infant Abortion may occur in women with mumps in the first trimester of pregnancy. It is not common and probably not caused by direct viral damage to the fetus. The connection between primary endocar- dial fibroelastosis and mumps remains vague. The disease’s declining incidence has been attributed to mumps vaccination. Some studies using reverse transcription polymerase chain reaction (RT-PCR) indicate that viral RNA can be amplified from myocardial samples in a high percentage of cases. However, the latter technique is open to contamination problems and hence this link remains to be con- firmed. Mumps virus has not been isolated from heart tissue at aut- opsy and these infants have no mumps antibody in their blood. They may show a delayed hypersensitivity response to the skin test. This has not been explained, but may reflect some immune defect in the fetus which could cause myocarditis and fibroelastosis.

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