Anticipating smallpox as a bioterrorist weapon

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ABSTRACT – The treat of bioterrorism means it is important to be able to diagnose smallpox. The responsibility for the initial recognition of cases lies with clinicians, and early diagnosis is the key to the successful control of an outbreak. Unless rapidly contained, a bioterrorist release of smallpox would constitute not just a national but a global threat to health. This brief review sets smallpox in its modern context as an infection potentially spread by bioterrorists and recommends sources of information from the twentieth century that will assist clinicians in diagnosing the disease.

KEY WORDS: anti-vaccinal immunoglobulin, antivirals, cell-cultured vaccine, differential diagnosis, laboratory diagnosis, lymph vaccine, patient isolation, ring vaccination, smallpox, vaccination

Introduction

Smallpox was declared globally eradicated in 1980. However, it is widely feared that the virus may have fallen into the hands of international terrorists. If so, it is important that any release into the community is recognised at the earliest possible moment lest its spread becomes uncontrollable. To ensure this, today's clinicians, few of whom have encountered smallpox, need to be aware of how it presents and what steps have to be taken to contain it.

Little was written about clinical or other aspects of smallpox in the latter half of the twentieth century, but there is plenty of descriptive writing from earlier times and this should enable smallpox to be quickly recognised. The historical record also contains descriptions of outbreak control procedures and discusses the pros and cons of vaccination. It has recently been argued that the great mobility of modern populations, and uncertainty about the ways in which smallpox might be released by bioterrorists, mean that previously well-tried control strategies need to be revised,¹ but what has not changed is the importance of diagnosing and isolating first cases of smallpox at the earliest opportunity, and of searching for concurrent and subsequent cases, and for contacts. A terrorist smallpox release is unlikely to be announced by the perpetrators, and any clinician, whether in general or specialist practice, may be the

first to see a case. All should therefore be able to recognise smallpox and know what action to take when they do so.

General sources of information

There are two compendia of smallpox, Dixon's *Smallpox*² and Fenner and colleagues' *Smallpox and its eradication*.³ The fact that they were written 40 and 20 years ago respectively does not detract from their value. The authors deal with smallpox as the global disease that it used to be: Dixon describes the history of smallpox on every continent; Fenner *et al* document the inception, progress and outcome of the global eradication programme of the 1960s and 1970s. Fenner *et al*'s publisher (WHO) has now helpfully made their entire text available electronically.⁴

Clinical presentation

Smallpox is a prostrating illness characterised after two to three days of fever by a rash that is at first papular and then vesicular. In about 10% of cases there is an initial haemorrhagic rash with high associated mortality. Smallpox may at first be hard to distinguish from influenza and other fevers, and from chickenpox as the rash appears; but unless it is modified by previous vaccination, it is a more severe and prolonged illness than these infections.

Key Points

Early clinical recognition of smallpox is the key to outbreak control

Patient isolation and laboratory confirmation of diagnosis are essential first steps in clinical management

Smallpox in its unmodified form is a severe biphasic illness with fever followed after two to three days by a uniformly developing rash; there may be early haemorrhagic or late secondary complications

The clinical presentation of smallpox may be greatly modified both by past and recent vaccination

Smallpox vaccination may be effective, both pre- and post-exposure, but the scale of its pre-exposure use must be determined by a continuing risk assessment of the likelihood of bioterrorist release, of the state of clinical and public health preparedness to recognise and isolate cases, and of the possible risks to vaccinees and their close contacts especially when there is mass vaccination

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Compared with chickenpox its rash is more uniform and evolves more slowly (see Fig 1 for further differences).

Of the many clinical descriptions of smallpox available, that by Wilkinson is worth quoting both because it emphasises the biphasic nature of the disease, at first toxic and/or haemorrhagic and then eruptive, and because it so well describes how overwhelming smallpox may be from the beginning.⁵

The incubation period of twelve days is followed by a sudden onset with rigor, fever, vomiting, headache and backache. These are the outstanding symptoms of the toxic phase, which usually lasts three days. If the patient survives this phase the fever abates and with its decline the focal [ie skin] lesions begin to appear. The secondary fever which accompanies maturation of the pustules is distinct from the fever of the toxic phase and is usually considerably lower ... The toxic phase may be heralded by the appearance of a prodromal petechial rash, the petechiae appearing usually on the axillary folds, in the flanks and in the groins. Or the prodromal rash may be morbilliform, scarlatiniform or even urticarial in character. If the toxic phase is severe enough to kill, death usually occurs on or before the sixth day, and it is common to find failure of development of focal lesions in these cases ... A patient suffering from toxic smallpox presents an unforgettable picture – the extreme prostration, the generalised tonelessness, the expressionless face with its blood-clotted lips and intelligent eyes, and the skin, either leaden-hued from haemorrhage or lobster-red from universal erythema, make these patients stand out in vivid contrast to their fellow victims covered with focal lesions. The mental clearness which is retained to the end is one of the most striking clinical features.

Wilkinson's account is based on almost a thousand cases seen in Hong Kong between November 1937 and July 1938, but there are other descriptions derived from even more extensive experience, for example when smallpox was last epidemic in Britain in the early 1900s.^{6,7} There is also a 'how to diagnose' monograph based on an analysis of several thousand cases observed in London in 1901–2.⁸ A more recent and discursive description of smallpox appears in the first three editions of Christie's *Principles and practice of infectious diseases*.⁹

Differential diagnosis

Smallpox may be difficult to diagnose either because it presents as a haemorrhagic disease that is fatal before any eruptive skin lesions develop or, at the other extreme, because it is greatly modified by the attenuating effect of past vaccination(s). Cases in the pre-eruptive phase are probably not infectious, or scarcely so.¹⁰ However, the sparse skin lesions of vaccine-modified smallpox in an ambulant patient have often been misdiagnosed in the past and become the source of outbreaks of smallpox.^{11,12} This attenuation of clinical smallpox does not signify any loss of virulence on the part of the virus.

Initial cases of smallpox in the community have been misdiagnosed as chickenpox, measles, secondary syphilis or scarlet fever. Of these infections only chickenpox is now common in developed countries, but smallpox has also been diagnosed as other, non-infectious, skin eruptions. Conversely, during an outbreak, other diseases have been thought to be smallpox

(Table 1). What generally should distinguish smallpox is the prodrome of high fever and intense headache, backache and vomiting followed by a uniformly evolving vesicular rash. That is the presentation now to be expected in a population which for the most part has never been vaccinated, or if they were it was at least 30 years ago.

Laboratory diagnosis

Since the global eradication of smallpox, there have been important advances in the laboratory diagnosis of rash-associated infections, including smallpox. By electron microscopy (EM), a pox virus can be rapidly recognised while it is abundant in the vesicular fluid and this remains the primary diagnostic tool.¹³ Though polymerase chain reaction (PCR)-based tests can differentiate smallpox virus even from the very similar vaccinia virus,^{14,15} and though PCR is also more sensitive than EM, it should for the moment still be seen as a research procedure able to confirm rather than make the diagnosis.

While both EM and PCR procedures can be performed on inactivated samples, the well tried tests that in the past have been used to distinguish smallpox virus from other pox and herpes viruses depend on propagation of the virus, usually on the chorioallantoic membrane of fertile eggs. After two to three days this procedure allows smallpox to be differentiated on sight from herpes simplex, vaccinia and cowpox viruses. However, the propagation of smallpox virus must be strictly limited on safety grounds, with laboratory investigations to confirm or exclude smallpox being done by fully vaccinated and trained staff working, as soon as a pox virus diagnosis is confirmed, at containment level 4. Each bioterrorist target country needs to decide how a suspected case of smallpox can best be investigated in a secure laboratory in such a way that the correct diagnosis can be quickly arrived at under effective containment.

Treatment

It is misleading to refer to smallpox treatment, as once the disease is established none is known to be effective; however, post-exposure vaccination can prevent or mitigate smallpox, and antivaccinal immunoglobulin¹⁶ and antivirals may also have a prophylactic role. While the value of the latter two is still unproven, post-exposure vaccination, promptly and competently

Table 1. Differential diagnosis of smallpox – the ten most common other diagnoses referred as smallpox to a London receiving station in 1902. The percentages are out of 607 unconfirmed cases referred at the same time that 7,235 cases were confirmed by station medical officers as smallpox.⁶

Chickenpox	203 (33.4%)	Syphilis	30 (4.9%)
'Skin disease'	74 (12.2%)	Lichen	26 (4.3%)
Measles	48 (7.9%)	'Erythema rheumatica'	13 (2.1%)
Acne	42 (6.9%)	Urticaria	12 (2.0%)
Eczema	31 (5.1%)	Scabies	11 (1.8%)

Fig 1. The classic rashes of smallpox (left) and chickenpox (right). The rash of smallpox shown is at about one week's development, with the pocks uniform, semi-confluent on the face, and also distributed over the extensor surface of the arm. The chickenpox rash shown is earlier in disease; the pocks are at all stages of evolution and mostly on the trunk. Difficulties can arise in distinguishing these diseases. However, in the pre-eruptive stage the patient is much more acutely ill and febrile in smallpox, and there may at first be a general erythematous rash, or a purpuric rash in the groins or axillae. On the other hand, a previously vaccinated person may have a greatly modified smallpox rash with only a few ill-developed pocks, and only be mildly ill. This last may easily be mistaken as a case of chickenpox and readily give rise to secondary cases. It must be recognised for what it is – smallpox. (Reprinted with permission from Elsevier (Anderson *et al*¹⁰).

done, has saved many lives. Vaccination is most effective when done within three days of exposure in the previously unvaccinated and within seven days in the previously vaccinated, as may be inferred from studies by Hanna and others.¹⁷ These time constraints mean that there must be contingency planning if post-exposure vaccination of populations is to be at all effective against a bioterrorist release of smallpox. It is because it is doubtful whether those exposed to a well disseminated release could be vaccinated in time that the dilemma of deciding how extensive pre-exposure vaccination should be has now to be confronted.

There appears to be no experimental animal model that closely enough resembles human smallpox to allow satisfactory therapeutic studies. However, if prophylactic vaccination is re-introduced, experiments on volunteer vaccinees would be able to throw more light on the use of immunoglobulin and

antivirals in the treatment both of disseminated vaccinia and, by analogy, of smallpox virus infections. *In vitro* studies of the activity of antivirals on vaccinia and, under strict containment in the official WHO repositories of smallpox virus, on smallpox infected cells would also be justified.

Pre-exposure vaccination

The key to smallpox prevention is still Jennerian vaccination, and so important is it now considered to maintain the capacity for mass vaccination that in the USA and elsewhere governments are urgently renewing vaccine stocks. New stocks will not be of lymph vaccine but of vaccines grown *in vitro*, eg in Vero and MRC5¹⁸ or, in the case of the UK, probably chick embryo cells. It is hoped that these vaccines will be less reactogenic than vaccine lymph.

A single pre-exposure vaccination with lymph, properly done, is believed to be largely protective thereafter from death from smallpox; but the side effects, as confirmed in a recent trial,¹⁹ are not negligible, whether the very common complaints of fever and malaise 7–10 days post vaccination (Table 2) or the far rarer serious complications. If smallpox vaccine ever has to be used on a scale that will effectively forestall a future terrorist attack, it will be important to minimise these unwanted effects; but in a population mostly being vaccinated for the first time they will not be wholly avoidable. An account of the major complications of lymph vaccination is given in GS Wilson's classic *Hazards of immunisation*;²⁰ no information is yet available on the extent of the side effects of the cell-cultured vaccines now in preparation.

Nor is it yet determined whether cell-cultured vaccine will be as protective as vaccine lymph. Both the choice of vaccinia strain to be cultured *in vitro* and the extent of its attenuation by passage have recently been the subject of technical debate but, for obvious reasons the protectiveness of these new vaccines can only be determined indirectly, for example by challenge with a lymph vaccine and by immunological studies.

Smallpox control by patient isolation

In the UK, the second half of the nineteenth century saw bitter struggles over compulsory infant vaccination, and between its introduction in 1853 and the insertion into the Vaccination Acts of a clause allowing conscientious objection in 1907, some cities refused to accept compulsory vaccination.²¹ Instead of seeking to achieve herd immunity through vaccination many thereafter began to build isolation hospitals outside their conurbations, a trend from which emerged the twentieth century smallpox control policy of voluntary vaccination backed up by *post hoc* 'ring' vaccination and adequate provision of isolation beds. Whenever smallpox broke out there would be vigorous case finding and isolation, with vaccination of every identifiable contact.²²

Table 2. Common complaints following primary smallpox vaccination: percentage frequency of reactions to lymph vaccine: 665 subjects were observed at 7–9 days and at 10–12 days. More than a third missed work, school, sleep or recreation as a consequence of the vaccination (data taken from Frey *et al*).¹⁹

Complaint	7/9 days (%)	10/12 days (%)
Fever	8.9	5.3
Headache	40.6	38.0
Muscle aches	50.4	42.7
Chills	17.7	15.5
Nausea	14.0	11.9
Fatigue	47.7	42.9
Pain at site	76.5	76.7
Lymphadenopathy	30.5	53.8
Rash elsewhere	5.6	10.1

In the UK, this approach was successful in containing importations of smallpox in the twentieth century, even though infant vaccination rates fell below 50%. On the other hand, indigenous smallpox had by then been eradicated and importations were usually of single cases, so that these control measures were never as seriously challenged as they would probably now be as a consequence of a bioterrorist release. Latterly, there was also emergency mass vaccination in response to public alarm at the occurrence of cases of smallpox, though it is doubtful whether this materially influenced the course of what were, with few exceptions, very modest outbreaks. In the face of a disseminated terrorist release of smallpox, emergency vaccination might assume much greater importance though it would also present a huge logistic challenge.

The present threat of bioterrorist smallpox to their largely unvaccinated populations means that target countries such as the USA and the UK are actively reviewing their vaccine stocks, and even considering re-introduction of routine voluntary vaccination as a necessary if unwelcome expedient. The reasons are: the likelihood that a bioterrorist release of smallpox would be covert, diffuse and not immediately recognised; the fact that modern society is highly mobile and people would not be amenable to necessary measures that would interrupt their business and social movements, probably for days at a time; and a tacit acknowledgement that surveillance, and the facilities for proper management of cases and observation of suspected cases and contacts, might very well be inadequate to contain a bioterrorist release. For these reasons general vaccination, upon which little reliance was placed in the UK during most of the twentieth century, might now become an important pre-exposure public health initiative.²³ Lymph vaccines generally conferred medium term (2–10 years) protection from disease, and long-term protection from death from smallpox. If cell-grown vaccines can match this and their side effects are shown to be minimal, it might soon be decided to offer pre-exposure vaccination on a wide scale, particularly if the bioterrorist threat intensifies.

Conclusion

The two most important contributions that the clinician can make are to 'think smallpox' and, should they arrive at that provisional diagnosis, to immediately isolate the patient at the scene and seek laboratory confirmation. In the UK, the means of obtaining expert clinical and laboratory confirmation of smallpox are available to any doctor who might encounter a suspected case,²⁴ and even were smallpox vaccination to be reintroduced, there would remain many who, for various reasons, would remain unvaccinated and susceptible to it. Secondary spread from unrecognised cases (particularly likely to occur in general hospitals) is an outcome that must be avoided by taking prompt steps to recognise, confirm and isolate cases, and protect contacts by post-exposure vaccination.

This article has cited several venerable papers, written from long experience of smallpox and vaccination, which show acute-ness of observation and challenge the attitude that only recent

medical writing deserves to be studied. However, smallpox is now also a topical issue and so new data are becoming available.²⁵ Unless the bioterrorist threat recedes, smallpox awareness will have to be sharpened and some difficult decisions taken about the use of vaccine. Uncontained, a smallpox release in the UK or elsewhere would rapidly become a global threat to health.

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