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Review Article

# Atypical Measles Syndrome - A Brief Review

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**Abstract**

A brief review of the atypical measles syndrome is presented. In addition to the clinical aspects of the disease, including the differences with classical measles, the biologic features of the condition will be described. A series of queries relating the syndrome will then be raised and, whenever possible responded to. Thus, it appears that the atypical measles syndrome is possibly not contagious. Immune complexes formation may be critical to the pathogenesis of this disease. This condition is not often severe and very rarely fatal. This syndrome may be exceptionally related with the live attenuated anti-measles vaccine. In spite of a common belief on the absence of immune waning, it is possible that humoral waning may play an important role in the atypical measles syndrome.

## INTRODUCTION

Atypical measles syndrome (AMS) is a form of measles infectious disease which differs from classical measles by an older age distribution, often by a polymorphous skin involvement, by nodular pulmonary infiltrates, by hepatic abnormal functions and by eosinophilia [1]. Originally described in conjunction with a killed measles virus (MV) vaccine in 1965, it is still occasionally reported to the present day, decades after this vaccine was banned in 1967 [2].

In addition to drawing the attention of the medical community to the persistence of this syndrome, I will attempt to answer several queries that have arisen, concerning the AMS features: are the AMS patients contagious? Does the immunological set-up of AMS differ from that of classical measles? Can this syndrome be severe or even fatal? Is the AMS also related with types of vaccines different from the formalin-inactivated MV vaccine (FIMV)? What happened with the later vaccine since its exclusion in 1967? What is the role of the waning immunity against the MV in the development of the AMS?

### Atypical Measles Syndrome

This variant of measles was described in 1965 by Rauh and Schmidt [3] as atypical measles, mainly in adolescents and young adults. These patients had been formerly vaccinated with the FIMV, available since 1963, and then exposed to wild type MV (wt MV) [1]. The clinical features of AMS differed to such an extent from those of classical measles, that the physicians failed to make the connection and the diagnosis was often missed. They may include a high and prolonged fever, a polymorphous eruption, starting in the hands and feet [4], hilar lymphadenopathy and nodular pulmonary consolidations, with or without pleural effusion. The pulmonary nodules may persist for several weeks to years. Antibody titers to measles antigens in AMS are usually higher than 1:160, which is unusual for typical measles [5].

The AMS patients' nodules may resolve spontaneously and abruptly. This is very rarely the case for tuberculosis, sarcoidosis, histoplasmosis or metastatic cancer, which represent the main differential diagnostic conditions [5].

Additional symptoms of AMS include abdominal pain, abnormal liver function tests (perhaps with hepatitis), edema and headache. Koplik spots are infrequent, so are cough and dyspnea.

Due to the dissimilarity with the symptoms and the biology of classical measles, the diagnosis of AMS may be missed completely or postponed until a random serologic test points out to the diagnosis [5]. A report from 1987 on 291 adults with measles, revealed a number of features unusual for classical measles. Liver function tests were abnormal in 86% of the patients; abdominal pain, diarrhea and vomiting were described in one third of the cases; musculoskeletal complains were often found, some with raised CPK levels; Koplik spots, found in 188 of the patients persisted 5-7 days, instead of 2 days after the rash, as for typical measles; photophobia was present in 1% only. Retrospectively, these patients would be diagnosed as AMS, with some support from the fourfold increased antibody titer by hemagglutination inhibition [6].

### Are the AMS Patients Contagious?

Since measles is probably the most contagious human viral disease, this is expected to be also the case for AMS. This would moreover represent an additional and occult source of MV dissemination and an obstruction to the global efforts to

eradicate this infection.

However, as no publication regarding the eventual transmissible or contagious character of AMS, was retrieved, it is not excluded that this condition may be non-contagious. The pathogenesis of AMS as described below sustains an immune, but perhaps not infective basis for this condition.

### Are the Immunological Features of AMS Distinct?

One of the earliest pathogenetic hypotheses suggested was that a very strong cellular immune reaction is initiated for AMS to develop [7].

We have seen that, based on the antibody titer, by complement fixation, a level higher than 1:160 is more in favor of AMS [5,8]. In 1999, AMS was duplicated in 2 of 5 macaques [9], which developed petechiae on the skin and lung infiltrates, rich in eosinophils and in immune complexes and with vasculitis. The suggested pathogenesis, at least in macaques, included a primary response to non-protective type 2 CD4+ T-cells. The same scientists later showed that antibody reactions were both short-lived and deprived of avidity maturation. Submission of the animals to wt MV caused an anamnestic production of antibodies with low avidity, which may be at the origin of the immune complexes previously described [10]. In spite of the challenge infection, overt transmissibility in the macaques with atypical measles was not reported [9,10].

### Can AMS Be As Severe as Classical Measles and can it be Fatal?

Severe cases of AMS have rarely been described [1], although prolonged chest X-ray abnormalities have raised some concern [5]. Patients may look very ill, but spontaneous recovery is the rule. Only one description of a fatality from AMS was suggested and it has not been confirmed [11].

### Is AMS Related also with Types of Anti-MV Vaccines Different from the Formalin-Inactivated MV Vaccine?

Although most cases of recognized AMS are associated with the FIMV, several patients have developed the disease after clearly defined, previous live attenuated vaccine (LAV) [5]. This occurrence is not easily accounted for. The discussion below concerning the putative role of the immune waning, will attempt to grasp the pathogenesis of these cases.

As FIMV was banned in 1967, and considering it may have taken several months to dispose of all the stocks, a relatively small proportion of AMS cases may have been vaccinated with LAV, or with both FIMV and LAV during the transition period. Isolated reports on AMS occurring without a clear history of vaccination have also been released [2].

### What Happened with the Formalin-Inactivated MV Vaccine, after it was banned in 1967?

The FIMV induced specific immunity which was transient and, in addition, predisposed to a sporadically serious disease, the AMS. In contrast, the LAV, which had been developed since 1963, showed promising results, in term of sustained protection.

For a short while, sporadically, LAV was supplied following a previous FIMV administration with relatively good combined results [7].

In 1967, the FIMV was withdrawn from the shelves progressively, mainly due to insufficient antibody titers, but also because of the superior results of the LAV. It is not improbable that pockets of the FIMV continuous use persisted for an undefined period, accounting for some of the more recent cases. However, this cannot explain cases of AMS occurring as late as 2015 [2].

### What is the Role, if any, of Immunity waning in the Pathogenesis of AMS?

Waning of the MV-specific immunity has been suggested not to occur [12,13]. However, such a statement must specify whether one is dealing with humoral or cellular immunity or with both. It must include, in addition, the type of anti-MV vaccination used, the age of the individual at vaccination and if a natural MV exposure was recorded.

In spite of the vaccination policy, late exposure to MV occurs also in unvaccinated subjects and in young adults with waning immunity [14].

Classically, AMS was related with a previous vaccination with FIMV which was protective for several months only [15]. But antibody titers dropped subsequently quite abruptly [3]. If an infective challenge with wt MV was administered, AMS might develop. This deterioration of the antibody titers is none other than a humoral immunity waning. Hence it is not remote to speculate on a different type of immune waning that may explain the development of AMS in cases with prior LAV. In these instances, antibody titers decline, meaning secondary vaccine failure, which has also been shown to occur [16]. This may follow a prolonged or excessive exposure to a measles patient. In the context of the universal two-dose vaccination, such an event may be rare. On the other hand, in individuals without vaccination and with no history of measles, one must speculate on an asymptomatic exposure to MV. Although very rare, this may raise the production of low to moderate titers of anti-MV antibodies.

In any case, a secondary exposure to the wt MV may carry two possible consequences. On the one hand, this may boost a specific immunity. In the absence of this secondary exposure, the chances are in favor of an immunity waning. On the other hand, if such an exposure is allowed in young adults with waning immunity, this may lead to AMS, even with a background of LAV.

Reports on classical measles occurring several years after universal 2-dose LAV vaccination (secondary vaccine failure) have confirmed the evidence of humoral waning [18].

Levine et al studied the prevalence of anti-MV antibodies, 20 years after the introduction of the 2-dose MMR vaccination to Israel. Thus in 2007, the samples from 18-19 year-old recruits were positive in 85.7%, as compared with 95.6% in 1996. The decline was similar, irrespective of gender, years of education, smoking habit, but it occurred only in Israeli born subjects [19]. The authors discarded the option of a waning immunity, possibly under the influence of the literature precept

## DISCUSSION

The diagnosis of AMS is difficult. It is often missed given

a lack of consideration. Atypical measles syndrome contrasts with the classical disease by several features, possibly related to an immune complex formation. This may perhaps account for the putative absence of transmissibility in AMS. Although this variant of measles may infrequently be severe, it has rarely been reported to be fatal.

Predominantly associated with the FIMV, AMS may occur much less frequently with LAV or even with a complete lack of vaccination. However, it is not excluded that the withdrawal of the FIMV may have been more gradual than previously thought.

The specific immune mechanisms in AMS, based on the macaque model, involve probably immune complexes formation. It is suggested in this review, that immunity waning, mainly humoral immunity, plays a common role in the pathogenesis of all forms of AMS. It is of note, that as AMS occurs at an age older than the classic age for measles, it may represent an unusual late host response model to a common infectious agent.

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