Is there any relationship between extra-pulmonary manifestations of *Mycoplasma pneumoniae* infection and atopy/respiratory allergy in children?

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**Abstract**

*Mycoplasma pneumoniae* is a common cause of respiratory infections in children, but sometimes extra-pulmonary diseases can be observed. The immunological mechanisms involved in these extra-respiratory complications are unknown. Here, we report a small case series of *Mycoplasma*-related diseases including 5 children who developed: i) aseptic meningitis; ii) urticarial rash and pericardial effusion; iii) pleural effusion with severe eosinophilia; iv) Stevens-Johnson syndrome; v) multiform erythema. Interestingly, all children were moderately to highly atopic, as a common immunologic feature.

**Case Report #1**

Patient 1 was a 7-year-old boy who presented to our Emergency Pediatric Department because of high fever, persistent headache and vomiting. As neck rigor was observed, a lumbar puncture was performed: the cerebrospinal fluid resulted to be sub-limpid, showing a significant pleocytosis, but both bacterial cultures and viral genome research (with particular regard to herpesviridae) were negative. However, as the parents reported some episodes of upper airway inflammation during the previous weeks, thus serology for MP was evaluated, demonstrating a high titer of specific IgM (>27 AU/mL). Whereas the initial therapy with ceftriaxone and acyclovir rapidly improved patient’s clinical condition. Unexpectedly, the most relevant finding of the blood test presented normal values of cellular turnover parameters (LDH: 456 U/mL, b2-microglobulin: 0.9 mg/mL) and of liver and kidney function. A wide diagnostic work-up for infections and autoimmunity was performed: particularly, no autoantibody was showed and stools examination did not showed intestinal viral, bacterial or parasitic infections. The only significant serology was related to MP, through a very high specific IgM titer (>27 UA/mL). The treatment with clarithromycin led to a complete resolution of both symptoms and laboratory abnormalities: indeed, eosinophilia gradually decreased to normal values (500/mm3).

**Case Report #2**

Patient 2 was a 13-year-old girl having urticaria (which responded to anti-histamines and steroids only partially), diffuse arthralgia and dactylitis-like transient fingers edema. Therefore, the patient received to several diagnostic investigations including heart ultrasound, which showed a pericardial effusion greater than 0.5 cm. Eye examination did not show uveitis and autoantibody panel was completely negative; however, serum IgM against MP was present (20 AU/mL). After therapy with oral clarithromycin was started, a ready clinical improvement occurred.

**Case Report #3**

Patient 3 was a 10-year-old boy who was evaluated at the Pediatric Emergency Department because of acute onset of upper abdominal pain, vomiting and mild fever. Chest X-ray showed an interstitial pattern of lung inflammation associated with a very mild pleural effusion. Unexpectedly, the most relevant finding of the blood count was leukocytosis (WBC: 11750/mm3) with severe and absolute eosinophilia (5750/mm3). The clinical exam revealed no clinical signs of proliferative disease and blood test presented normal values of cellular turnover parameters (LDH: 456 U/mL, b2-microglobulin: 0.9 mg/mL) and of liver and kidney function. A wide diagnostic work-up for infections and autoimmunity was performed: particularly, no autoantibody was showed and stools examination did not showed intestinal viral, bacterial or parasitic infections. The only significant serology was related to MP, through a very high specific IgM titer (>27 UA/mL). The treatment with clarithromycin led to a complete resolution of both symptoms and laboratory abnormalities: indeed, eosinophilia gradually decreased to normal values (500/mm3).

**Case Report #4**

Patients 4 was a 10-year-old boy who was admitted to the pediatric ward in order to receive intravenous nutritional and hydration support, because of the onset of severe ulcerative mucosal lesions involving lips and oral cavity, in addition to the anal area. Such a clinical picture was diagnosed as being Stevens-Johnson syndrome with prevalent mucosal involvement. After an...
Discussion and Conclusions

Several studies have linked respiratory MP infections to asthma exacerbations and there are some evidences that MP might elicit a Th2 immune response in the bronchial system. As regards MP-related extra-pulmonary complications, although those are supposed to be immune-mediated/autoimmune phenomena, the immunological mechanism—or mechanisms—is unknown. Here, through the description of our case series, a potential association between this category of reactive diseases caused by MP and atopy might be highlighted.

A tendency to IgE production during the acute phase of MP respiratory infections has been previously described and specific IgE against this microorganism could be detected. Stelmach I et al. observed several antibody and cellular immune parameters in children affected with respiratory infections, but their data did not show a significant difference in total serum IgE levels between MP positive and negative patients. Actually, a trend toward a mild and gradual increase of IgE levels was described during the first year after mycoplasma infection. However, in our case series, we could observe a much greater IgE elevation in these children affected with MP-related extra-pulmonary diseases compared to the data displayed in the aforementioned study. All these observations might raise the speculation that the predisposition to produce IgE in some individuals, namely atopy, and/or the coexistence of respiratory allergy might predispose to (or might be involved in the pathogenesis of) extra-pulmonary diseases related to MP acute infections. Of course, although the method used to measure MP serology showed a good reliability, serology diagnosis of MP infection should be cautiously considered and comparative studies will be required to support this preliminary observation.

References

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Table 1. Immunologic parameters in patients with extra-pulmonary disease related to Mycoplasma pneumoniae.

| Parameter                  | Case #1 | Case #2 | Case #3 | Case #4 | Case #5 |
|----------------------------|---------|---------|---------|---------|---------|
| Blood count, µL            |         |         |         |         |         |
| Leucocytes                 | 6100    | 11500   | 11750   | 9950    | 8200    |
| Neutrophils                | 1700    | 5300    | 1700    | 3300    | 6100    |
| Lymphocytes                | 3300    | 5300    | 3600    | 4900    | 1500    |
| Monocytes                  | 500     | 600     | 350     | 800     | 500     |
| Eosinophils                | 600     | 300     | 5700    | 800     | <100    |
| Basophils                  | <100    | <100    | 250     | 150     | <100    |
| Immunoglobulins            |         |         |         |         |         |
| IgA, mg/dL                 | 143     | 162     | 155     | 181     | 93      |
| IgG, mg/dL                 | 810     | 864     | 1011    | 1030    | 688     |
| IgM, mg/dL                 | 87      | 104     | 82      | 108     | 56      |
| IgE, U/mL                  | 648     | 168     | 900     | 431     | 1028    |
| Complement, mg/dL          |         |         |         |         |         |
| C3                         | 110     | 147     | 172     | 153     | 126     |
| C4                         | 31      | 27      | 39      | 23.8    | 24.5    |
| Lymphocyte count, %        |         |         |         |         |         |
| CD3                        | 68      | 55      | 66      | 62      | n.a.    |
| CD4                        | 37      | 36      | 36      | 31      | n.a.    |
| CD8                        | 17      | 23      | 23      | 21      | n.a.    |
| CD19                       | 15      | 25      | 21      | 17      | n.a.    |
| CD16/56                    | 10      | 16      | 10      | 14      | n.a.    |