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Acute Keratoconjunctivitis Resulting from Co-infection with Avian Newcastle Virus and Human Adenovirus

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Abstract

Purpose: To report a case of human keratoconjunctivitis caused by both Newcastle disease virus (NDV) and human adenovirus.

Methods: A 32-year-old-man presented with an acute unilateral keratoconjunctivitis that resolved with corneal scarring. On presentation, his conjunctiva was swabbed for metagenomic sequencing (MDS).

Results: The highest number of pathogen sequencing reads in the conjunctiva sample mapped to the NDV. The second highest number of reads mapped to human adenovirus. Confirmational testing with directed reverse-transcription polymerase chain reaction also identified NDV in the specimen.

Conclusions: Newcastle's conjunctivitis has not been reported in over forty years. Mixed infections, including zoonotic pathogens may be more common than realized.

As interest in cross species infectious disease transmission increases, detailed exploration into ocular surface infections can shed light into these zoonotic diseases. Newcastle disease virus (NDV), also called avian pneumoencephalitis, is a highly contagious frequently fatal viral illness that infects birds. Symptoms in birds are often dramatic and include diarrhea, ataxia, paresis, wheezing, dyspnea and sudden death. It is very rare for Newcastle disease to affect humans. When it does, the symptoms are primarily ocular and present as a diffuse conjunctivitis. Systemic symptoms in humans are rare with headache, fever and malaise rarely being reported. Human respiratory symptoms or pneumonia have not been documented with human transmission. In all reported cases of human Newcastle virus conjunctivitis, there has been known exposure to infected birds. The last case of ocular infection with NDV conjunctivitis involved a laboratory technician and was published in 1976. In this case, her conjunctiva was exposed to droplets created during the grinding of an infected chicken[1]. In this report, we describe a man with no known bird exposure who was diagnosed with a co-infection of Newcastle's and adenoviral keratoconjunctivitis.

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CASE REPORT:

A 32 year old man presented to the Aravind Eye Clinic in Madurai India with a five day history of left eye swelling, severe irritation, and decreased vision. His occupation was a painter. He had no known sick human contacts and no known poultry contact. His right eye was not affected. His uncorrected visual acuity of the left eye measured 20/30. The slit lamp examination was remarkable for left side conjunctival inflammation and coarse superficial punctate corneal lesions with a “stuck on” appearance. Bacterial cultures demonstrated no growth. Because of the corneal lesions, the patient was given a presumptive clinical diagnosis of microsporidia keratoconjunctivitis. He was treated with topical fluconazole and ciprofloxacin. Upon follow up, his left eye acuity decreased to 20/80 as the keratitis resolved with central anterior stromal opacity. Upon presentation, the patient provided informed consent to participate in a conjunctivitis metagenomic sequencing pilot trial. In this study, we recruited patients presenting with acute, less than fourteen days, of symptomatic conjunctivitis. This study was IRB approved at the University of California San Francisco and Aravind Eye Hospital. This patient’s left conjunctiva was swabbed, per protocol for metagenomic deep sequencing as previously described[2]. Metagenomic RNA deep sequencing identified both *avian avulavirus 1* (Newcastle virus [NDV]) and human adenovirus type 8 (HAdV-D8) (Figure 1). Orthogonal testing was performed with directed reverse-transcription polymerase chain reaction (RT-PCR) using previously described NDV primers[3]. Sanger sequencing of the amplicon confirmed the presence of NDV RNA in the patient’s sample. The presence of adenovirus was confirmed at the Stanford Clinical Virology Laboratory (CLIA-certified).

DISCUSSION

Reports of Newcastle conjunctivitis are rare[4] and have not appeared in the published literature in the last 45 years. Prior reports of human ocular involvement described conjunctivitis only and those affected have had known involvement with poultry research or industry[5]. Although the NDV vaccine was one of the first vaccinations to be introduced into the poultry industry, numerous local and international hurdles limit its widespread implementation[6]. Chickens are particularly susceptible to this virus, though wild birds can also be infected with NDV. Outbreaks of NDV remain a problem in both the poultry industry and non-domesticated birds. In this report, the patient’s occupation was not poultry related. As he painted buildings, it is conceivable he was exposed to bird droppings, secretions or any variety of a sick wild bird during outdoor painting. Detection of both NDV, an RNA paramyxovirus, and adenovirus, a double stranded DNA virus, in this case was unexpected. While it was possible that adenovirus was the main driver of his acute and severe symptoms, the “stuck-on keratitis” noted on slit lamp examination is uncommon for either virus and is more commonly attributed to microsporidia keratoconjunctivits. However, microsporidia is readily detectable by deep sequencing and was completely absent from in this sample[7]. As keratitis has not been described in the historic Newcastle literature, we think it is likely NDV contributed to the robust conjunctivitis and it is more likely the adenoviral infection resulted in anterior stromal scarring. Fortunately, his right eye was never affected. Because deep sequencing techniques are prone to environmental contaminations and are sensitive to the bioinformatics pipeline parameters, orthogonal testing is routinely done to limit false

results. The use of directed RT-PCR on the sample provides confirmation of the presence of NDV in the patient's conjunctiva. Newcastle disease virus, is an RNA paramyxovirus and an example of a zoononotic infectious disease, meaning it can jump from a non-human host to a human. As interest in cross species infectious disease transmission increases, this case illustrates occurrences may happen more frequently than we realize. Furthermore, coinfection of viruses represents opportunities for deep recombination of genetic materials, across viral kingdoms and even between RNA and DNA viruses[8]. The unbiased nature of metagenomic deep sequencing diagnostics is not only beneficial for the diagnosis of atypical and unexpected conjunctivitis pathogens but may also provide another source of insight into drivers of pathogen evolution.

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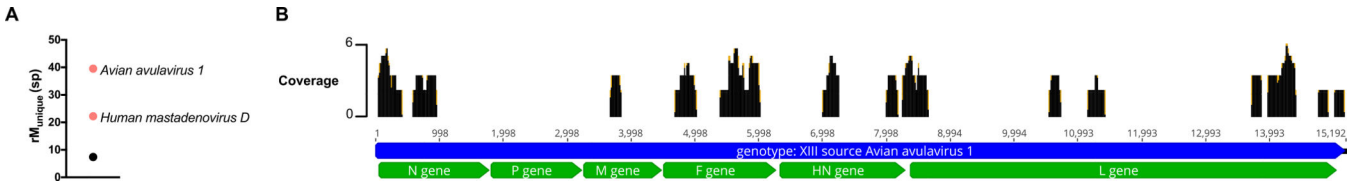

Figure 1:

Metagenomic RNA deep sequencing of the patient's conjunctival sample. (A). The y-axis indicates the normalized abundance of unique sequencing reads (rM = reads per million reads). In this sample the *Avian avulavirus 1* Newcastle virus (NDV) represents the most abundant sequence in this sample. The human adenovirus D RNA sequences represented the second most abundant unique sequencing read in the sample (B) Genome coverage of *avian avulavirus 1* as identified with metagenomic RNA deep sequencing. The x-axis represents the position along the *avian avulavirus 1* genome in base pairs. Beneath the x-axis, in green, are the positions of each gene in the genome as obtained from the NCBI reference sequence entry NC_039223.1. The y-axis represents the absolute number of reads that map to the indicated position in the genome.