Fatal Adenovirus Infections in Infants Probably Infected with HIV†

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Abstract

Adenovirus infections occur commonly in infants and children but are rarely fatal. Although immunosuppression has been associated recently with fatal outcome of adenovirus infections, reports of major morbidity or mortality caused by adenovirus infection in HIV positive patients are infrequent.

This is the first report on fatal adenovirus infections in presumably HIV - positive infants in Thailand. Three infants, aged 4, 8 and 5 months, were hospitalized with diagnoses of pneumonia and ARDS, pneumonia with hepatomegaly and ARDS, and pediatric AIDS with pneumonia, respectively. All the infants died within a few weeks after hospitalization. Serologic tests revealed positive anti - HIV in all three infants. Unfortunately, no additional investigation for definite diagnosis of HIV infection was employed.

Pathological findings from autopsy and post mortem needle biopsies revealed adenovirus pneumonia in the first two infants, and massive adenovirus infection of the liver in the third infant. Diagnoses were based on characteristic light microscopic pathological findings, and demonstration of viral particles arranged in crystalline arrays in the nucleus of the infected cells by electron microscopy.

Adenovirus infection occurs in all age groups, with a wide spectrum of diseases, but is often self-limited and rarely fatal. It is common in preschool children, and is responsible for upto 10 per cent of cases of bronchiolitis and viral pneumonia(1). However, severe disease rarely occurs in immunocompetent individuals(2). Recent evidence indicates that immunocompromised hosts may have more severe adenovirus disease with fulminant or disseminated, and may be rapidly progres-

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sive and fatal. The fatal adenovirus infection has been reported in patients immunocompromised by intensive chemotherapy for malignancies, in bone marrow, kidney and liver transplants, primary immunodeficiency and severe combined immunodeficiency diseases in both children and adults[3-14].

Adults infected with human immunodeficiency virus (HIV) has been reported to carry adenovirus[15,16]. However, reports of fatal adenovirus infection are rare.

In Thailand, the positive isolation rate of adenovirus from nasopharyngeal secretion of pediatric patients attending the out-patient department with symptoms of respiratory tract infection during the rainy season was 5.5 per cent for the overall age group, and 7.7 per cent for the age under 1.4 years[17,18]. In other unpublished reports, the rate of positive virus isolation ranged from 1.5 - 3.7 per cent in hospitalized children under the age of 2 years with symptoms of pneumonia and bronchiolitis. No documented mortality resulting from adenovirus infection has been previously reported.

This is the first report of morbidity and mortality caused by adenovirus infection among presumably HIV - positive infants, in Thailand.

MATERIAL AND METHOD

Records of 847 autopsies from 1987 to 1994, and 116 post mortem needle biopsies from 1991 - 1994 on infants and children were reviewed for evidence of adenovirus and HIV infections.

Cases with clinical diagnosis and/or pathologic diagnosis of extensive pueumonia and pathologic diagnosis suspicious of adenovirus infection, based on characteristic histopathological findings on routine light microscopic examination were selected and reviewed.

Routine H & E slides from those selected were reviewed. Additional slides were cut when necessary. For identification of adenovirus, all available paraffin-embedded-tissue of suspicious cases were processed and examined under a transmission electron microscope.

Histochemistry stains for acid - fast - bacilli (Kinyoun's carbol fuchsin), fungi (Gomori's methenamine silver, Periodic - acid - Schiff stain, and Mayer's Mucicarmine stain) and Giemsa stain were performed on available tissues in searching for possible associated infections.

Exclusion of possible infections caused by cytomegalovirus, herpes simplex virus and *Pneumocystis carinii* were also made by immunohistochemistry study using paraffin - embedded - tissues, available in some cases.

Determination of anti - HIV using ELISA, gel particles agglutination (PA) test and western blot techniques, were performed only on some living patients suspicious of having HIV infection.

Surveillance for AIDS death in infants has been carried out at the Institute of Pathology since 1990. All available samples of heart blood obtained from infants at autopsy were determined for Anti - HIV using similar techniques.

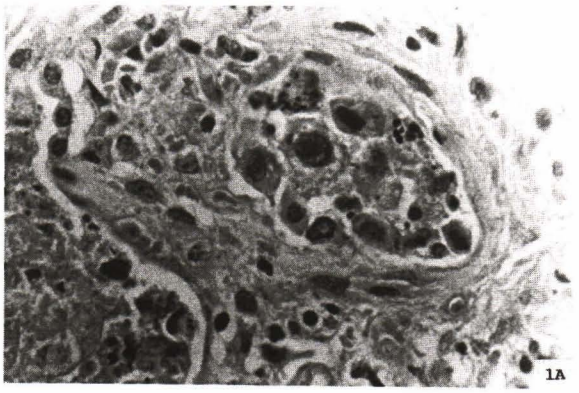


Fig. 1A. Light microscopy of lung showing necrotizing bronchiolo-alveolitis with presence of smudge nuclei and intranuclear inclusions within the pneumocytes. H&E x 132 (Case 1).

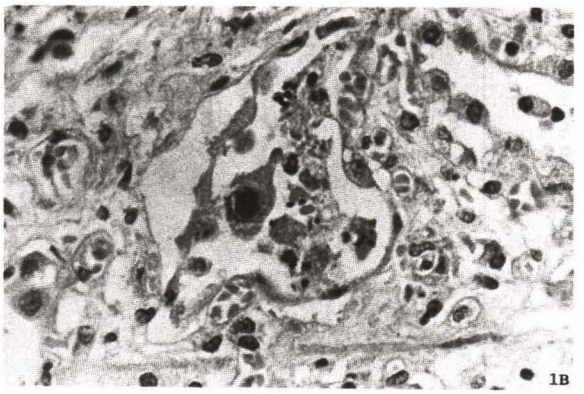


Fig. 1B. Prominent Cowdry type A intranuclear inclusion within the pneumocytes. H&E x 132 (Case 1).

Table 1. Summary of clinical informations on HIV positive infants with fatal adenovirus infection.

Clinical data	Case 1	Case 2	Case 3
Age/Sex	4m/F	8m/M	5m/M
Body weight	4.5 Kg.	5.7 Kg.	4 Kg.
Month/Year	August 1991	April 1992	October 1994
Clinical presentation			
-Symptoms	Chronic cough and fever	Chronic cough followed by fever	Recurrent cough and fever
-Signs	-Progressive dyspnea	-Progressive dyspnea	-Failure to thrive
	-Hepatosplenomegaly	-Hepatosplenomegaly	-Dyspnea
			-Hepotosplenomegaly
Chest x-rays	Extensive alveolar infiltration of lungs	Diffused alveoar infiltration of lungs	Progressive infiltration of both lungs, (mixed interstitial and alveolar)
Clinical diagnosis	Pneumonia and ARDS	-Massive pneumonia with ARDS	-Pediatric AIDS
		-Hepatosplenomegaly	-Progressive pneumonia
			-Hepatosplenomegaly
Hospital stay	24 days	29 days	22 days
Anti HIV test	Positive (ELISA and PA) (heart blood)	Positive (ELISA and PA)	Positive on admission (ELISA and PA)
Familial history of HIV infection	Not available	Not available	Available (positive) just prior to hospitalization
Remarks	SGOT/SGPT 56/42	SGOT/SGPT 41/15 on early admission	-Mother positive for Anti HIV
			-No liver function test available

Table 2. Summary of pathological examination and findings on presumably HIV-positive infants.

Case No.	Type of pathological examination	Pertinent post mortem findings			Remarks
		Light microscopy	Immunohistochemistry (Immunoperoxidase)	Electron microscopy	
1.	Full autopsy	1. Diffuse necrotizing bronchio alveolitis, with presence of intranuclear inclusions and smudge nuclei in all lobes of lungs (Fig. 1A,B)	-Negative for CMV	-Demonstration of round to polygonal virions, of approximately 70 mm. in diameter arranged in cystalline arrays characteristic of adenovirus, in pneumocytes and bronchiolar lining cells (Fig. 2 A,B)	No virus culture
		2. *Pneumocystis carinii* pneumonia RLL	-Positive for *Pneumocystis carinii*		
		3. Severe fatty change of liver			
2	Needle biopsy of lung and liver	1. Lung : Necrotizing bronchioalveolitis with presence of intranuclear inclusions and smudge nuclei (Fig. 3A,B)	-Negative for CMV.	-Demonstration of characteristic adenovirus as in case 1 (Fig. 4)	No virus culture
		2. Liver : Presence of intranuclear inclusions and smudge nuclei -severe fatty change (Fig. 5)		-Demonstration of characteristic adenovirus in hepatocytes (Fig. 6)	
3	Needle biopsy of lung and liver	1. Lung - unsuccessful biopsy (no lung tissue)			
		2. Liver - Multiple foci of coagulative necrosis of hepatocytes, with presence of intranuclear inclusions and smudge nuclei in surrounding hepatocytes. (Fig. 7A and B)	-not performed (limited biopsy tissue)	-Demonstration of hexagonal virions, of 70 mm. in diameter, in crystalline arrays charactaristic of adenovirus, in hepatocytes. (Fig. 8)	No virus culture

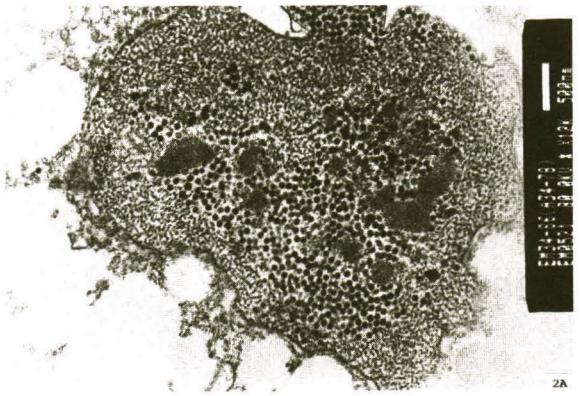


Fig. 2A. Electron micrograph of lung demonstrating intranuclear viral particles within the pneumocytes. X 12,000 (Case 1).

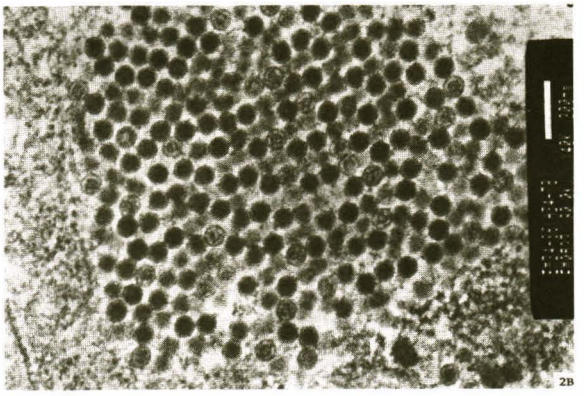


Fig. 2B. Higher magnification of 2A demonstrating viral particles, around 70 nm in diameter, in crystalline arrays. X 40,000 (Case 1).

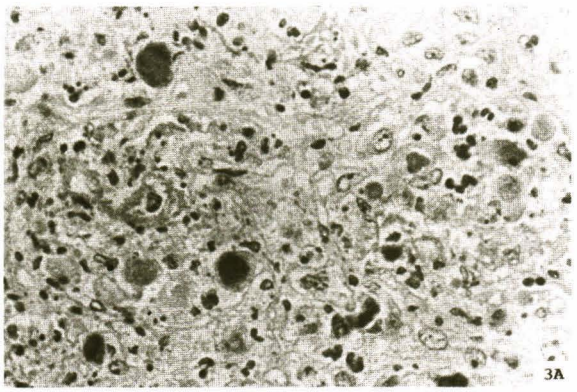


Fig. 3A. Light microscopy of lung biopsy showing extensive bronchiolo-alveolitis, and scattered cells with smudge nuclei. H&E x 132 (Case 2).

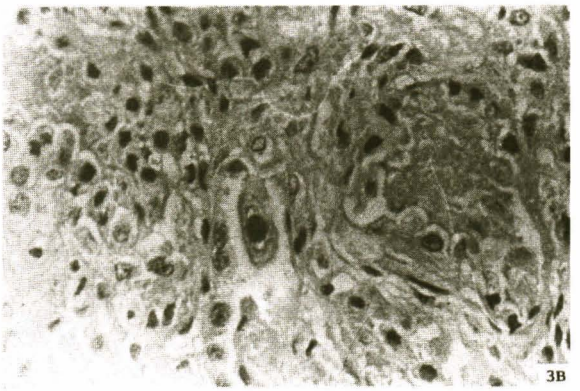


Fig. 3B. Light microscopy of lung biopsy demonstrating Cowdry type A intranuclear inclusion within the pneumocytes. H&E x 132 (Case 2).

RESULTS

Among the 15 infants and young children who had fatal adenovirus infection, there were 3 infants who probably had evidence of HIV infection.

The clinical information and pathological findings of all 3 infants are summarized in Tables 1 and 2, respectively.

The characteristic light microscopic findings of adenovirus pneumonia originally described by Goodpasteur[19] are shown in Figures 1 and 3.

The characteristic intranuclear inclusions and smudge nuclei in hepatocytes are demonstrated in Figures 5 and 7.

The characteristic adenovirus particles of 60-70 nm in diameter arranged in crystalline arrays[20,21] are shown in electron micrographs, Figures 2, 4, 6 and 8.

DISCUSSION

Opportunistic viral infections in persons with HIV infection have been well described[22-37].

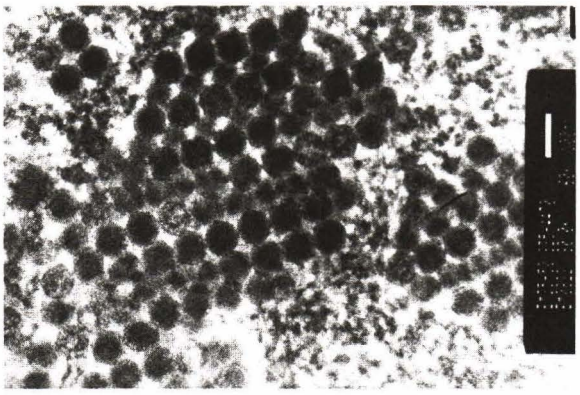


Fig. 4. Electron micrograph of lung biopsy demonstrating hexagonal viral particles, approximately 70 nm in diameter. X 60,000 (Case 2).

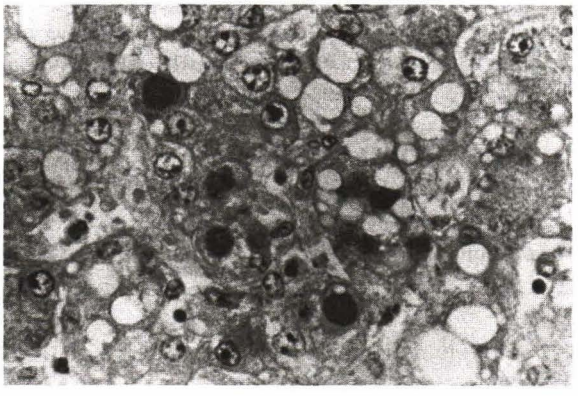


Fig. 5. Group of hepatocytes containing smudge nuclei and intranuclear inclusion, with fatty change. H&E x 132 (Case 2).

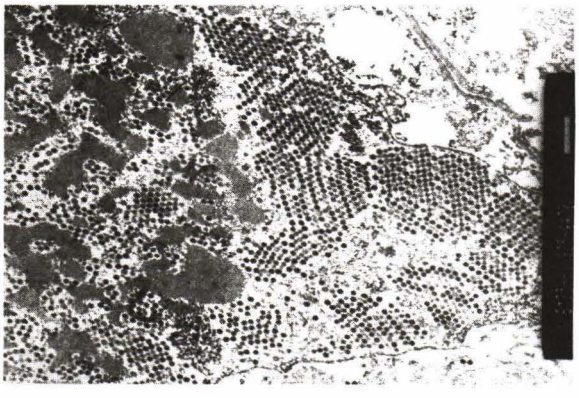
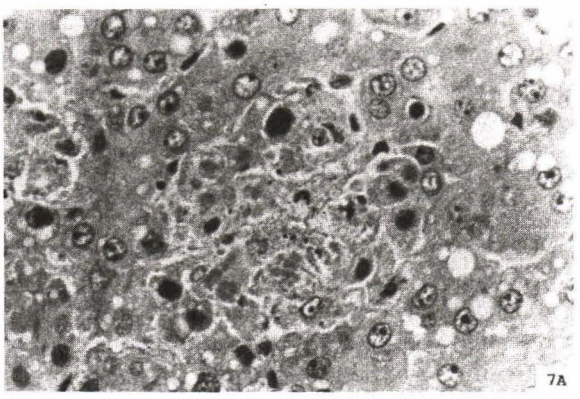


Fig. 6. Electron micrograph of hepatocyte showing intranuclear viral particles in crystalline arrays. X 10,000 (Case 2).



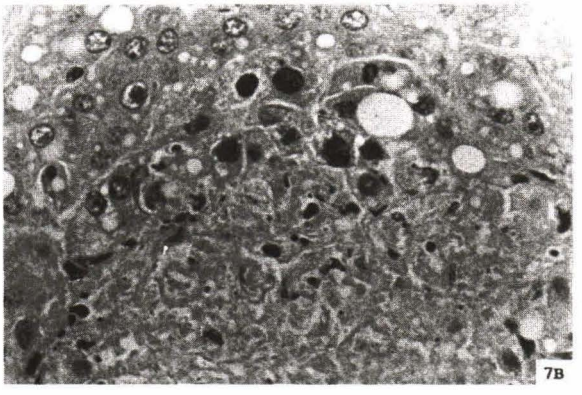


Fig. 7A, B. Light microscopy of liver biopsy showing Cowdry type A intranuclear inclusion, and smudge nuclei, bordering liver necrosis. H&E x 132 (Case 3).

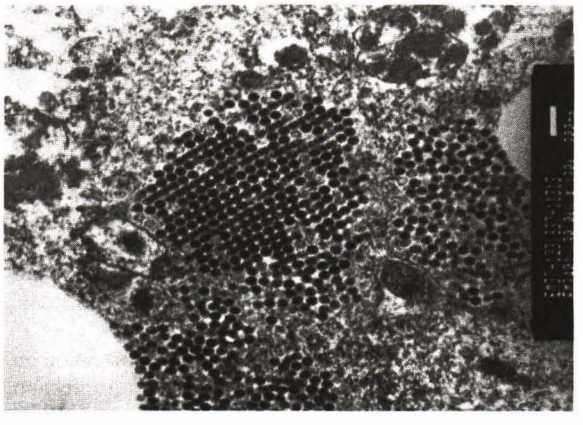


Fig. 8. Electron micrograph of liver biopsy showing numerous viral particles, 70 nm in diameter, in crystalline arrays. X 20,000 (Case 3).

Reports of morbidity or mortality caused by adenovirus among this patient population are uncommon despite the frequent isolation of adenoviruses from patients with HIV infection[15,16].

Some HIV - infected adult patients with diarrhea have adenovirus colonic infection[38-40]. Adenovirus infection of the duodenal mucosa has been described as a cause of intractable diarrhea in a middle aged woman with terminal acquired immunodeficiency syndrome (AIDS)[41]. There are a few reports describing the pathological features of necrotizing adenovirus infection of the renal tubules in adult AIDS at terminal stage[42,43].

Although adenovirus is a common cause of pediatric respiratory illness, it has been rarely associated with major morbidity or mortality in HIV- infected children. Only a few children with HIV infection have been described as having disseminated and fatal adenovirus infection with striking extensive hepatic necrosis[6,44].

All of the three present cases had clinical evidence of extensive pneumonia, two of them (Case 1 and Case 2) were confirmed by pathologic findings as having disseminated adenovirus pneumonia. Case 1 also had *Pneumocystis carinii* infection which is a common opportunistic infection, in the right lower lobe. In Case 2, adenovirus was demonstrated in both lungs and liver.

Because the autopsy was restricted to needle biopsy, lung involvement and the extent of dissemination could not be fully defined in Case 3. The liver involvement with hepatic necrosis in Case 3 was most likely caused by viral dissemination or overwhelming infection, since adenovirus seems to have a predilection for hepatocytes in patients with some forms of immunodeficiency and disseminated adenovirus infection[6,10,44].

With the high prevalence of adenovirus infection in humans and increasing numbers of HIV infection among children via vertical transmission, it is likely that cases of disseminated and fatal adenovirus infection will continue to be seen in young children. It seems not overemphasized to call for attention in terms of early diagnosis and effective therapy for this serious opportunistic infection which has been proved to be rapidly fatal in severely immunosuppressed patients.

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โรคติดเชื้ออะดีโนไวรัสที่รุนแรงถึงตายในเด็กที่สงสัยว่ามีการติดเชื้อ เอช ไอ วี†

*ดำรงค์ พันธุมโกศล, พ.บ.**

การติดเชื้อ อะดีโนไวรัส พบได้บ่อยในเด็กเล็ก แต่ไม่รุนแรงถึงตาย ผู้ป่วยภูมิคุ้มกันบกพร่องจากสาเหตุอื่น ๆ อาจติดเชื้ออะดีโนไวรัสรุนแรงถึงตายได้ แต่รายงานที่กล่าวถึงพยาธิสภาพหรือการตายอันเกิดจากอะดีโนไวรัสในผู้ป่วยเอดส์ทั่วโลกมีน้อยมาก

ได้ศึกษาผู้ป่วยเด็กอายุต่ำกว่า 1 ขวบ จำนวน 3 ราย ที่สงสัยว่ามีการติดเชื้อ เอช ไอ วี และติดเชื้ออะดีโนไวรัสร่วมด้วยจนถึงแก่กรรมเนื่องจากปอดบวมอย่างรุนแรง ผลการตรวจศพและชิ้นเนื้อทางพยาธิวิทยา พบอินคลูชันบอดี้ ซึ่งมีลักษณะเฉพาะของการติดเชื้ออะดีโนไวรัสในปอดและตับโดยกล้องจุลทรรศน์ปกติ ตรวจยืนยันโดยกล้องจุลทรรศน์อีเล็กตรอน พบไวรีออน ซึ่งมีขนาดและลักษณะเฉพาะของอะดีโนไวรัสในชิ้นเนื้อผู้ป่วยทั้ง 3 ราย เป็นรายงานแรกที่มีการตีพิมพ์ในประเทศไทย

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