Clinicopathological Conference Report

Looking beyond Allergic Bronchopulmonary Aspergillosis in a 10-year-old Boy

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CHIEF COMPLAINT

A 10-year-old male child presented with chief complaints of cough, breathing difficulty, and fever for 15 days.

HISTORY OF PRESENTING ILLNESS

The child presented with cough that was progressive, productive (greenish-brown sputum), and with no diurnal variation. Breathing was progressive, more in supine position, and he preferred to sit hunched forward. There was high-grade, intermittent fever (102°F) with one or two spikes per day. There was no history of hemoptysis, chest pain, passage of greasy stools, allergy, atopy symptoms, or contact with tuberculosis.

PAST HISTORY

There were recurrent episodes of cough and breathing difficulty from 1 year of age (1–2/year requiring Rx). This intensified after the age of 5 years, requiring hospitalization, IV medication, and nebulization and inhalers. He was diagnosed as allergic bronchopulmonary aspergillosis (ABPA) 2 months back and given itraconazole, steroid, and nebulization.

FAMILY HISTORY

He had one older sibling (age, status not mentioned). Father was a truck driver till 5 years back, farmer since then. There is no history of tuberculosis in the family members.

Birth

No significant history

Development

Normal profile

Immunization

Immunized till 5 years of age.

Treatment

Patient was admitted in Beas Hospital, Amritsar, on Nov 23, 2016. Chest X-ray (CXR) and computed tomography (CT) suggested bronchiectasis and necrotizing pneumonia. Treated with Co-amoxiclav ×3 days; then piperacillin-tazobactam + vancomycin ×4 days; hydrocortisone, itraconazole, and multiple nebulizations. Patient was referred to PGI after 10 days.

On examination: P = 160/minute, all pulses palpable; RR = 58/minute, blood pressure = NR, SpO₂: 88% in room air, 96% with oxygen.

Weight = 25 kg (<3rd centile), height = 122 cm (10th to 25th centile), OFC = 52 cm.

General examination: He had pallor and clubbing grade II. There were no cyanosis, icterus, lymphadenopathy, and signs of rickets.

Systemic examination: Respiratory system: Chest anteroposterior (AP) diameter increased, accessory muscles in use, suprasternal and lower intercostal recessions, percussion note resonant in all areas, liver dullness in 8th

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intercostal space, bilateral crackles and wheeze, R. infra-axillary breath sounds diminished, L. infraclavicular bronchial breathing. CVS: normal heart sounds, no murmur.

P/A: No organomegaly? tenderness in R. hypochondrium and epigastric region

CNS: NAD

Impression

- Bronchiectasis (CF vs non-CF) with ?ABPA, ?TB, ?HIV
- ABPA with acute exacerbation ?Bacterial, ?Fungal

Course: Child received oxygen, piperacillin-tazobactam + vancomycin + voriconazole and supportive management:

Pancreatic lipase, hypertonic saline, calories, protein, MCT oil, chest physiotherapy. He was given blood transfusion for anemia on Dec 09. Respiratory rate remained >50/minute, chest findings persisted, oxygen requirement persisted. On day 5, he developed increasing respiratory distress and pedal edema (but no hepatomegaly or raised JVP). On day 7, he had altered sensorium, E2M4V3, low K+, low blood sugar, worsening respiratory distress intermittent positive pressure respiratory (IPPR). Multiple episodes of desaturation and bradycardia (lack of IPPR), worsening shock, dopamine at 10 to 15 µg/kg/, in cardiorespiratory arrest, declared dead on Dec 08, 2016.

INVESTIGATIONS

	Date	Hb (g/dL)	TLC (/mm ³)	DLC (P/L/M/E)	Platelets (/mm ³)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)	ESR (mm)
Pre-PGI	27/11	11.1	29,000	75/15/07	779,000	77.4	77.3	78.0	76.4	
	29/11	11.0	26,800	80/15/04	794,000	24.6	24.4	24.7	24.2	
	01/12	10.0	40,500	92/05/02	750,000	31.8	31.5	31.7	31.6	
	02/12	9.7		91/05/03	894,000	11.3	11.8	11.3	9.6	
PGI	04/12	9.1	222,800		796,000					
	06/12	9.0	32,290	88/08/04	494,000	72.7	22.8	31.4	15.0	QNS
	09/12	7.8	30,200		496,000					
	10/12	11.5	29,860	85/09/04/1	375,000	73.3	23.4	31.9	17.8	116
	12/12	8.0	35,210	70/24/01/4	138,000	84.6	23.2	27.4	17.8	

04/12: PT = 17 seconds (12–14 seconds), INR = 1.27, aPTT = 31 seconds (24–30), Ddimer+

		Na ⁺ /K ⁺ /Cl ⁻	Urea/Creat	AST/ALT/ALP	Prot/Alb	S. Bil	Ca/PO ₄	CRP
Pre-PGI	27/11	121/2.5/87						
	29/11	131/3.4/93						
	01/12	134/2.5/91						
	02/12	138/2.5/NA						
PGI	03/12	134/2.2/93	12/0.70	47/48/NA	NA/1.5			
	06/12	130/3.5/90	24/0.54	25/31/180	6.2/1.4	<1.0,<0.1	7.8/4.3	335.3
	10/12	136/4.4/95	33/0.60	38/16/229	7.1/1.6	<1.0,<0.1	NR/NR	NR
	11/12	139/3.9/101	42/1.00					
	12/12	137/3.8/100	45/0.90					

06/12	HIV	Nonreactive
06/12	Sweat chloride	Inadequate sweat
07/12	Stool for fat globules	40–50/hpf
08/12	Blood culture	Sterile
08/12	Sputum culture	Pseudomonas aeruginosa. S: Imipenem, Piptaz, Ciproflox, Ceftazidime Amikacin. R: Netilmycin
06/12	Sputum GeneXpert	No M. tb
07/12	AFB smear (5440)	No AFB seen
08/12	AFB culture (BT3707)	No Mycobacteria after 42 days
09/12	AFB culture (BT3723)	No Mycobacteria after 42 days
12/12	AFB smear	No AFB seen
06/12	Immunoglobulin profile (mg/dL)	IgG = 1660 (540–1610), IgA = 376 (70–250), IgM = 51 (50–180)
06/12	IgE	2022 KU/L (<85)
06/12	NBT (Unstimulated/Stimulated)	Pt: 30%/95%. Control 04%/90%. Not consistent with CGD
06/12	Asp. Fumigates-specific IgE	No reagent/14.2 KUA/l
06/12	Galactomannan index	0.18
08/12	Aspergillus skin test	Negative
08/12	2D Echo	Normal heart, No sig. PAH, PAsystpr = 25 mm Hg, No effusion

(Cont'd...)

(Cont'd...)

		pH	pO ₂	pCO ₂	HCO ₃	BE	Na ⁺ /K ⁺ /Cl ⁻	Glu/Lac	AG	cCa
04/12	V	7.578	42.0	62.1	56.7	31.6	136/2.3/92	67/3.7	-14.2	1.19
09/12	A	7.414	39.6	47.5	29.3	5.4	132/3.9/98	87/2.2	4.0	1.11
11/12	A	7.169	108	92.4	36.0	4.2	140/3.0/102	15/1.7	5.7	1.23
11/12	A	7.151	98.2	127	24.8	2.4	138/2.6/101	193/2.4	6.8	1.20
12/12	A	7.618	105	56.9	57.6	32.2	136/2.3/98	93/3.5	-20.6	1.14
12/12	A	6.992		117	19.0	-3.8	142/3.8/112	64/3.1	2.3	1.35

CXR: Consistent with bronchiectasis; CT chest: Consistent with bronchiectasis.

FINAL DIAGNOSIS

Immediate cause: Severe pneumonia with bronchiectasis

Antecedent cause: Cystic fibrosis with ABPA

DISCUSSION**Approach to the Case**

- What is the basic diagnosis?
- Is there ABPA?
- What organism(s) is/are expected in the lungs?
- What is the cause of death?

What Is the Underlying Diagnosis?

- Recurrent pneumonia
- Greenish-brown sputum
- Clubbing
- Hyperinflated chest
- Crackles and wheeze
- Bronchiectasis
- Pseudo Bartter picture
- Respiratory failure
- *Pseudomonas* in sputum
- Allergic bronchopulmonary aspergillosis

All these features suggest a possibility of cystic fibrosis (CF)

Lung Pathology in CF

- Bronchiolitis
- Bronchitis
- Bronchiolar obliteration
- Bronchiolectasis
- Bronchiectasis
- Bronchiectatic cysts, emphysematous bullae, sub-pleural blebs
- Areas of fibrosis
- Bronchial arteries enlarged and tortuous
- Secondary pulmonary hypertension

What Else Can Be Expected in CF?

- Pancreas: Fibrosis, Pancreatitis
- Liver
- Sinuses
- Vas deferens

- Hypertrophic osteoarthropathy-arthritis
- Fibrosing colonopathy (strictures)
- Edema-hypoproteinemia
- Amyloidosis
- Aquagenic palmoplantar keratoderma (skin wrinkling)

Is Anything Missing?

- Failure to thrive ±
- No symptoms/signs of pancreatic insufficiency
 - Malabsorption
 - Rickets
- Laboratory confirmation

Criteria for diagnosis of cystic fibrosis are
- Clinical features of any of these systems (respiratory / gastrointestinal / genitourinary system) OR h/o CF in sibling OR +ve newborn screening test

AND

- Two elevated sweat chloride OR two CF mutations OR abnormal nasal PD

Although CF was not proven, it seems to be the most likely diagnosis

Alternate Causes of Bronchiectasis

Postinfectious bronchiectasis: TB, bacterial, viral	
Immune deficiency: primary/secondary	X
Primary ciliary dyskinesia (PCD)	X
α1-Antitrypsin deficiency	X
Gastroesophageal reflux disease (GERD)	X
Allergic bronchopulmonary aspergillosis (ABPA)	
Connective tissue diseases	X
Inflammatory bowel disease	X
Rare: hematological malignancy	X
Idiopathic: 30–70%	

Non-CF Bronchiectasis in Indian Children

- N = 80 cases over 7 years
- Postinfective (measles, varicella, bronchiolitis or pneumonia): 14%
- Post-TB: 10%
- PCD (suspected): 15%

- ABPA: 7.5%
- PID: CVID 2, Pan-hypogammaglobulinemia 2, CGD 1 6%
- HIV infection: 1%
- Malformations: 4%
- Repeated aspiration: 2.5%
- Misc: Foreign body: 1, SJS: 1, Asthma: 1 4%
- Cause not identified: 36%

Has TB Been Ruled Out?

- PGIMER Pediatric Pulmonology Unit data (12 months)
- TB suspected in 94; diagnosed in 52; AFB in 40 (GL = 27, BAL = 10, BAL and GL in 3, LN = 2, Pleural fluid = 1)

Detection of AFB in Gastric Lavage (Cumulative Percentage)

Yield of AFB from BAL in Gastric Lavage Negative Cases

Yield of AFB from BAL in Gastric Lavage Negative Cases

No. of GL Samples Tested	No. of Children Tested	BAL Positive (No. of children)
2 samples	4	0
3 samples	18	4
4 samples	6	2
5 samples	4	0
6 samples	9	3
7 samples	2	0
8 samples	0	0
9 samples	1	1
Total	44	10

TB (in addition to CF) not ruled out with the work-up done

Is there ABPA?

ISHAM Criteria

- Predisposing conditions
 - Bronchial asthma, cystic fibrosis

- Obligatory criteria (both should be present)
 - Immediate hypersensitivity to *Aspergillus* Ag OR elevated IgE against *Aspergillus fumigatus*
 - Elevated total IgE (>1000 IU/mL)
- Other criteria (≥2/3)
 - Precipitating or IgG antibodies against *A. fumigatus*
 - Radiograph findings consistent with ABPA
 - Total eosinophil count >500/mm³ in steroid naive pt

Radiological Staging

- ABPA-S (Serological ABPA)
 - Features of ABPA but no ABPA CT abnormality
- ABPA-B (ABPA with bronchiectasis)
 - Features of ABPA + bronchiectasis on HRCT
- ABPA-HAM (ABPA with high attenuation mucus)
 - Features of ABPA + high attenuation mucus on CT
- ABPA-CPF (ABPA with chronic pleuropulmonary fibrosis)
 - ABPA + 2 to 3 other radiological features (fibrosis, scarring, fibrocavitary lesion, aspergilloma, pleural thickening without presence of mucoid)

Criteria for ABPA in CF

Epidemiologic Study of Cystic Fibrosis (ESCF) criteria:

- Two of:
 - Immediate skin reactivity to *Af* antigens,
 - Precipitating antibodies to *Af* antigens,
 - Total serum IgE > 1,000 IU/mL
- and at least two of:
 - Bronchoconstriction,
 - Peripheral blood eosinophilia >1,000/μL,
 - History of pulmonary infiltrates,
 - Elevated specific IgE-*Af*/IgG-*Af*,
 - *Af* in sputum by smear or culture,
 - Response to steroids

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criteria

- Minimal diagnostic criteria
 - Clinical deterioration not attributable to other etiology.
 - Total IgE > 500 IU/mL
 - Immediate cutaneous hypersensitivity to *Aspergillus* Ag or elevated IgE level against *Aspergillus fumigatus*
- One of the following:
 - Precipitating Ab to *A. fumigatus* or Asp-specific IgG
 - New or recent abnormalities on chest radiography
- Classic case
 - Clinical deterioration not attributable to other etiology

- Total IgE > 1000 IU/mL
- Immediate cutaneous hypersensitivity to Aspergillus Ag or elevated IgE level against *A. fumigatus*
- Precipitating Ab to *A. fumigatus* or Asp-specific IgG
- New or recent abnormalities on chest radiography

How Common Is ABPA in CF?

- Systematic review and meta-analysis
 - Aspergillus sensitization 39.1% (CI 33.3–45.1); 41 studies
 - ABPA prevalence 8.9% (CI 7.4–10.7); 45 studies
- In Indian children with CF (n = 33)
 - Aspergillus sensitization 45.5%
 - ABPA 18.2% (CI 6.9% 35.4%)

What Organisms Can Be Expected?

Bacteria

- Early phase
 - *H. influenzae*, *S. aureus*
- Later phase
 - *P. aeruginosa*: 25% children, 70% adults
 - *Burkholderia cepacia* complex: 4% adults
 - *Stenotrophomonas maltophilia*: 15% adolescents
 - *Achromobacter xylosoxidans*: 6% adolescents, adults
 - Anaerobes

Bacteria in CF Children

- PGIMER Pediatric Pulmonology Unit data
- N = 89 children; 260 respiratory samples
- *Pseudomonas aeruginosa* 83 (55%)
- *Staphylococcus aureus* 35 (22%); 40% MRSA
- *Escherichia coli* 12 (8%)
- *Burkholderia cepacia* 12 (8%)
- *Acinetobacter baumannii* 8 (5%)
- 398 unique subtypes of *P. aeruginosa* (LES strain) from 10 pts

Fungi in CF

Mycobiome

- *Candida* species: *albicans*, *dubliniensis*, *parapsilosis*
- *Saccharomyces*
- *Malassezia* species
- *Aspergillus non-fumigatus* species
- *Aspergillus*, *Cladosporium*, *Scedosporium*, *Exophiala*
- During exacerbations
 - *A. fumigatus* (10–57%)
 - *Aspergillus* species: *niger*, *flavus*, *terrus*, *nidulans*
 - *Candida* species: *albicans*, *glabrata*, *krusei*, *parapsilosis*
- Disseminated *A. penicilliioides* in a 3-month infant with ?CF

Gupta K et al. *Pediatr Dev Pathol* 2016;19:506-511

- *Pneumocystis jirovecii*
 - Europe: 1.3 to 21.6%. Calderon EJ. *Med Mycol* 2010;48 Suppl1:S17-S20
 - Brazil: 13/34 (38%). Pederiva MA. *Med Mycol* 2012;50:556-560
 - France: 13/104 (12.5%). Hernandez F. *J Clin Microbiol* 2012;50:4107-410

Nontubercular Mycobacteria in CF

- Prevalence in CF: 3 to 23%
- Species
 - *Mycobacterium avium* complex (MAC) 75 to 95%
 - *M. abscessus* complex (subsp *abscessus*, *massiliense*, *bolletii*)
 - Rarer: *M. kansasii*, *M. fortuitum*, *M. goodii*
- Risk factors for NTM
 - *Aspergillus fumigatus* coinfection
 - ABPA
 - ? Excessive macrolide use

Viruses in CF

- Rhinovirus, Influenza A, B
- RSV, Parainfluenza, CMV, Adenovirus
- Viruses affecting lung function: CMV, HSV, EBV, VZV
 - Huang YJ. *Clin Chest Med* 2016;37:59-67, Frickmann H. *Eur J Microbiol Immunol* 2012;3:161-175
- 44 CF children; 92 sputum samples collected serially
 - Rhinovirus: 20
 - Adenovirus: 3
 - Influenza A, B: 3
 - Parainfluenza 1,2,3,4: 1
 - RSV, hMPV: 0
 - Coronavirus: 3
- Burns JL. www.influenzajournal.com 2012; 6(3): 218-223

What Is the Cause of Death?

Final Diagnosis

- CF with bronchiectasis with respiratory failure
 - *Pseudomonas* colonization/infection
 - *Aspergillus* colonization/infection
 - Other
- With Pancreatic insufficiency
- With ABPA
- With anemia and hypoproteinemia

Clinical Discussion

Prof S Varma: Thank you Dr Joseph. Please join me here
Good morning, during life as Dr Joseph has elucidated, clinical picture was fitting into cystic fibrosis (CF),

where 10-year-old child with cough, rapid breathing with regular exacerbation, and failure to thrive, both weight and height less than 3SD, clubbing and increased AP diameter. During admission, blood gas analysis showed hypochloremic alkalosis, imaging studies revealed bronchiectasis and sputum grew *Pseudomonas*. Clinically, it can be nothing other than CF. These children are known to have exacerbation and high predilection for colonization *Aspergillus* in this phase. *Aspergillus* sensitization is prevalent up to 40%; ABPA is there in 18% of children, matching with closest data from the All India Institute of Medical Sciences. Total IgE elevated as well as *Aspergillus fumigatus*-specific IgE elevated, there was no going away from ABPA. Ultimately what took away the child was pneumonia with any organism, most likely tuberculosis.

Treating unit SR: I'm the senior resident who was managing the case when the child was in ward. Child presented with characteristic chronic lung disease, our possibilities was CF with ABPA. Apart from the diagnostic algorithm which was shown in the presentation, facilities for mutation and sweat chloride were not available. Characteristic clinical features can be supported with blood gas analysis and stool for fat globules in resource-limited setting, and any of the two abnormalities, if present, the case can be labeled as suspected CF and management can be started in form of enzyme replacement therapy and soluble vitamin supplements. In view of rapid downhill course in this case, we suspected *Aspergillus* infection. A total of 11 to 15% of CF are associated with *Aspergillus*, out of them 30% are invasive aspergillosis, which can lead to rapid downhill course as is expected in this case.

Prof S Varma: There does not seem to be difference of opinion so far. Any other comments?

Dr Vivek (Nephrology): You have mentioned that probably next most common cause is idiopathic bronchiectasis. What is the usual age of presentation of these? If they present in early childhood, how can we clinically differentiate these from CF? Is there any urine analysis report?

Dr Pankaj Vaidhya (Pediatrics): A total of 30% of CF patients can have liver involvement in the form of biliary cirrhosis and venous congestion. Our case had hypoalbuminemia, although clinically only 3 to 4% have liver manifestations; we are expecting changes in liver.

Prof S Varma: It seems that there is no urine analysis report.

Resident (Pediatrics): Can it just be aspergillus-sensitive asthma? Is there any role of exhaled nitric oxide measurement in differentiating these two conditions?

Dr Meenu Singh: Although clinically classically fitting into CF, ways to approach these patients are different.

When these patients with bronchiectasis come to us, if there is bronchiectasis or features of airway obstruction, then we think more in terms of CF. ABPA is something that can occur in asthma; if they have uncontrolled asthma which can be colonized with *Aspergillus*, they can develop ABPA, leading to bronchiectasis and all the classical features, which can mimic CF. Only odd point is clubbing and growth retardation, which point toward lung suppuration. Sputum has grown *Pseudomonas* that also favors CF than ABPA with asthma and *Aspergillus*-sensitized asthma. Non-CF organisms like TB are unlikely. *Aspergillus* presents as colonization here, rather than hypersensitive response. In patients treated with steroids for a long time, this fungus tends to be invasive and one may get invasive aspergillosis.

Resident (Pediatrics): Exhaled nitric oxide has certain distinguishing value; it is not elevated in CF bronchiectasis.

Prof S Varma: Any new questions?

Dr Vignesh (Pediatrics): Although clinical manifestation fit into CF, lab findings do not fit into CF. Apart from CF, can we think of hyper IgE syndrome as we have increased IgE and can we go for STATA3 mutation?

Prof S Varma: I think we have discussed about this. That needs to be talked about later.

Resident (Pediatrics): My comment is about ultimate deterioration on day 5. The child was transfused on day 5; I do not know what was the chronology of deterioration and transfusion, I would like to keep a possibility of TRALI.

Dr Vignesh (Pediatrics): I would like to differ from basic diagnosis. I would like to keep primary immunodeficiency (PID) and workup needs to be performed. IgM is not normal in this patient, it was on lower side, i.e., at -2SD. IgG is very high. It might be one of the subclasses of PID. If one of these deficiencies is there, in lymph node biopsy we can see B-cell depletion.

Dr Mathew: Though one-third of patients can have liver disease, in this case, it does not suggest liver disease, because coagulation profile and enzyme levels are normal. Hypoalbuminemia can be explained by chronic malnutrition.

Prof S Varma: In the absence of urine examination, we cannot exclude amyloid in this child with recurrent infection for a long period of time.

Dr Joseph: I was also carried away with the IgE but hyper IgE syndrome includes not just bronchiectasis but also staphylococcal boils or pustule and that was not there in this particular child. IgG2 and IgG4 subclass deficiency cannot be ruled out till we have those values. Asthma starting as the primary diagnosis and in exclusion CF is unlikely for the reasons we have already mentioned. Transfusion started on day 5 and

deterioration started on day 7. So there was a 36 to 48 hours gap between the two events. There was an alteration in sensorium associated with hypoglycemia and hypokalemia, so either there is some metabolic cause for the initial deterioration or there is something in CNS which has not manifested clinically. I think despite the discussion, CF with this kind of presentation remains the first possibility in this child.

Prof S Varma: Let's see what Kirti has to show today.

Prof Kirti – Pathology Protocol

Partial autopsy was performed in this case. Patient was thin built and malnourished. All serous cavities were normal.

Lungs: Weighed 1,214 gm. Grossly, they are heavy and dull. Pleura had fibrinous tags. The mucosa over trachea and airways are dull and filled with secretions. Cut surface of the dull pleura is studded with multiple nodules ($8 \times 8 \times \text{cm}$) with multiple small breaking down abscess (more marked in the upper lobes). These are centered on airways and extending to surrounding lung parenchyma. Airways are dilated ($UL > LL$). Pneumatoceles are also present. Microscopically, there is extensive ulcerations of all order of airways, which are plugged with acute inflammatory cells, predominantly neutrophils with few eosinophils, accompanying mucus. Few giant cells are seen in the ulcerated lining (Figs 1A, B and 2A to E). No fungal hyphae are identified. There is florid bronchopneumonia with fibrinous and fibrous organization and formation of Masson bodies. In large areas, alveoli are filled with foamy macrophages, loaded with mucin. Edema and patchy alveolar hemorrhages are also noted. Branches of pulmonary veins show thrombi, and pulmonary artery shows features of pulmonary arterial hypertension with prominence of intra-alveolar arterioles (Figs 3A and B). All stains (AFB, PAS, modified AFB, Gram

and Gram–Twort's stain) do not show any organisms. PCR for *Mycobacterium* is negative. Lung tissue is negative for panfungal (including *Aspergillus*) gene.

Pancreas: Firm in consistency. Microscopically, there is extensive inter- and intra-acinar lobular fibrosis with few inflammatory cells, fat infiltration, and acinar atrophy. In addition, there is accumulation of PAS-positive eosinophilic secretions and dilatation of ducts and ductules. Prominence of Islets cells also noted (Figs 4A to D).

Liver: Weighs 900 gm. The capsular surface is essentially normal. Cut surface is soft. Microscopically, the lobular architecture is maintained. No steatosis or fibrosis is noted. Few portal tracts show portal inflammation with cholangiolar proliferation. Bile ducts are essentially normal. No increase in iron noted within hepatocytes (Fig. 5).

Gall Bladder: Normal.

Spleen: Weighs 90 gm. Grossly and microscopically they are within normal limits.

Heart: Weighs 110 gm. All valves and chambers are within normal limits. Except for mild RVH (0.6cm). Microscopically they are within normal limits.

Thymus: Normal for age.

Mediastinal lymph nodes: Enlarged (3–4 cm). Microscopically, focal necrotizing lymphadenitis with well-preserved T- and B-cell zones are noted.

Kidneys: Weigh 170 gm. Grossly, capsular surface shows mild hemorrhagic discoloration, along convex border. Cut surface shows medullary congestion. Microscopically, sclerosed glomeruli (more than expected for age) with immature glomeruli, features of acute pyelonephritis and ATN with granular casts are seen (Fig. 6).

Adrenals: Weigh 8 gm. Gross and microscopically are within normal limits.

Figs 1A and B: (A) Dull pleura with multiple nodules and fibrinous tags. Enlarged hilar lymph nodes are also seen; and (B) Mucosa over trachea and airways are dull. Multiple small breaking-down abscess (more marked in the upper lobes) centered on airways and extending to surrounding lung parenchyma are seen. The airways are dilated ($UL > LL$)

Figs 2A to E: (A) Inflammation accompanying the mucus glands of trachea; (B) extensive ulcerations of airways which are plugged with acute inflammatory cells, predominantly neutrophils with few eosinophils; (C) few giant cells are seen in the ulcerated lining, no fungal hyphae identified; (D) florid bronchopneumonia with fibrinous and fibrous organization and formation of Masson bodies; and (E) in large areas alveoli are filled with foamy macrophages, loaded with mucin. (hematoxylin and eosin, $\times 20$ – A, D, E; $\times 40$ – B, C)

Stomach, Esophagus, and Small and Large Intestines: Microscopically show increase in goblet cells in small and large intestine.

Testes: Vas deferens is absent (Figs 7A and B).

Bone Marrow: Normocellular for age.

Skin and Muscle: Within normal limits.

DNA of this patient was sent for 72 panel mutational analysis including most common Delta F 508; however, it was negative.

Final Autopsy Diagnosis (PM NO 27855)

- Histological findings are consistent with cystic fibrosis (negative for Delta F508 mutation)
 - Lungs – Central bronchiectasis, extensive confluent acute bronchopneumonia with organization
 - Pancreas – accumulation of secretions, chronic pancreatitis, fibrosis with atrophy
 - Liver – periportal cholangiolar proliferation
 - Vas deferens – absent

Figs 3A and B: Branches of pulmonary veins show thrombi. Pulmonary artery shows features of pulmonary arterial hypertension with prominence of intra-alveolar arterioles (inset) (hematoxylin and eosin $\times 40$)

Figs 4A to D: (A) Firm pancreas; (B) Extensive inter- and intra-acinar lobular fibrosis with few inflammatory cells, fat infiltration, and acinar atrophy; (C) Masson's trichrome stain reflects extensive inter- and intra-acinar lobular fibrosis with few inflammatory cells, fat infiltration, and acinar atrophy; and (D) Accumulation of eosinophilic secretions and dilatation of ducts (Inset: Alcian blue positive) (hematoxylin and eosin – B, C, Masson trichrome c, $\times 10$ – B, $\times 4$ – C, $\times 20$ – D)

- Features of pulmonary arterial hypertension and
- Acute pyelonephritis and acute tubular necrosis

Final Discussion

Dr Chakraborti: Dr Kirti, can you exclude completely ABPA in this case, since patient was on long-term steroids and demonstration of fungus is not essential in case of

ABPA, because it's not always seen. Moreover, patient was on itraconazole and voriconazole for a long time. Eosinophilic mucin is always not seen as allergic fungal sinusitis. Inspissated mucus is the basic morphology seen, otherwise if you see clinically patient with total and specific IgE raised, it favors ABPA. Examining at this point, what do you feel in this aspect?

Fig. 5: Portal tract reflects portal inflammation with cholangiolar proliferation (inset: CK7 IHC) (hematoxylin and eosin, $\times 20$)

Fig. 6: Acute pyelonephritis and ATN with granular casts (periodic acid-Schiff, $\times 20$)

Figs 7A and B: (A) Vas deferens absent and (B) seminiferous tubules and absent Vas deferens (hematoxylin and eosin, $\times 20$)

Prof S Varma: She may not be able to rule it out or rule it in.

Prof Sanjay Jain: I was listening to this debate between CF and ABPA. Let me tell you very frankly, clinicians have advantage of looking at the clinical parameter; there is no other situation if somebody has got B/L bronchiectasis and Pseudo-Bartter Syndrome. It has to be CF. How can you expect CO_2 to be 90% to be in a patient of asthma? This is a classic patient of bronchiectasis, there is no h/o wheeze. Asthma classically has cough, dyspnea, and wheeze. This patient had respiratory tract infection. ABPA sets in a setting of asthma. Where is the asthma? Component of bronchospasm and CO_2 retention does not occur. This is a classical Pseudo-Bartter Syndrome. How do you explain metabolic alkalosis? With due respect to microbiologists, this is not ABPA. This is CF whether or not you have genetic analysis. When there is diarrhea and metabolic alkalosis in a child, CF would be the diagnosis. Otherwise in a developing world, where the genetic analysis is not available, how would you diagnose CF without missing out?

Dr Ashish: Nice demonstration of pathology. Not finding any organism in lung is odd, when you have significant amount of neutrophilic exudates and all the respiratory

bronchioles are clogged. I look at it in two ways. On culture, on day 8 we grew *Pseudomonas* which is sensitive. Either we were doing it too well clinically in eradicating *Pseudomonas* or there is something wrong, otherwise *Pseudomonas* in CF is difficult to eradicate. Why are there giant cells?

Prof S Varma: Histology is a poor indicator of bacteria and this might be the reason.

Dr Meenu: This is in response to Dr Jain's comment. There is no doubt about CF. The doubt is whether there is ABPA. We still can not rule out. In fact it is, as Dr Chakrabarti mentioned. Hyperattenuated mucus is seen in ABPA as a secondary thing to asthma. In CF, mucus is very rich in DNA, as there are many neutrophils. Another thing is hyperattenuated mucus which is detected radiologically. I'm still doubtful, whether CF produces hyperattenuating mucus. So, ABPA is there, since the criteria are fulfilled. There are about 2,000 mutations; this patient might carry any of these. We are really impressed by pancreatic, testicular, and vas deferens changes, which is never seen clinically. How to detect it in ultrasound is always a problem.

Prof S Varma: When you are having hypersensitivity, it does not tell you where the organism is present. *Aspergillus*

in sinus could give rise to this picture. I mean to say that ABPA could not be ruled in or ruled out. We are at this moment dealing with pathology, i.e., definitely CF, we have test abnormalities that we need to explain. For that we do not have adequate explanation in lung as of now. We have not looked at the sinuses of this child. So, we can not say anything.

Dr Pankaj Vaidhya: This is regarding risk factor for progression of disease in children with CF and ABPA; as they grow older, they colonize *Pseudomonas* and along with poor nutrition status, the prognosis worsens.

Dr Kirti Gupta: Pathology also questions the existence of ABPA in this patient. Because bronchiocentric granuloma, allergic mucin, eosinophilic pneumonia were absent. Allergic mucin, charcot-Leyden crystals are not seen. Mucin was rich predominantly in neutrophils, not eosinophils. Regarding giant cells, they are predominantly foreign body type, produced in response to the destruction of elastic tissue of vessel wall and they are centered on bronchioles.

Dr Joseph: On the one hand, I'm pleased because the final diagnosis is similar to the initial diagnosis at the emergency. Two days later pulmonology unit also worked up on the same line. My own findings are not different from autopsy findings including pulmonary hypertension and wolffian duct abnormality. Mutation sometimes correlates with clinical phenotype; if it is very severe like if I have a homologous Delta508 deletion then the clinical picture pretty much looks like this. But the lung pathology and the changes need not correlate with the mutation, unless severe mutations are there. The fact that mutation study is not available did not take away from CF. Regarding ABPA, we should remember, the child has been treated with steroids and antifungals for the past 2 months, which might have changed the picture. Important thing is, adding ABPA in the diagnosis is that there is treatment for it. If it is there, we will add antifungals and steroids. The last comment is of course that, children with CF might have asthma-like symptoms (wheeze). Outside this institute, these cases are treated with bronchodilators and nebulizers, sometimes mislabeled as asthma. It is possible that fungal infection might have come from those nebulizers which were never cleaned.

Prof S Varma: We had excellent demonstration of CF. I'm not sure whether now ABPA is there despite treatment. I must complement the JR pediatrics for the enthusiastic participation in the discussion.

DISCUSSION

Cystic fibrosis is a genetic disorder driven by cystic fibrosis transmembrane conductance regulator (CFTR) mutations that affect the exocrine glands. It is an autosomal

recessive mode of inheritance. Twenty-five years ago, a variant (p.Phe508del; also known as F508del) in the CFTR gene was found to be the most common cause of cystic fibrosis. Historically, CFTR variants have been grouped into five (and sometimes six) functional classes. The class system provides a useful framework for understanding the primary defect at the cellular level.

A diagnosis of cystic fibrosis is based on the presence of clinical findings, along with an elevated sweat chloride concentration (>60 mM). The degree of organ system dysfunction varies considerably among affected individuals. Genetic modifiers and nongenetic factors both contribute to airway obstruction and infection with *Pseudomonas aeruginosa* – two traits that define lung disease in cystic fibrosis. The CFTR genotype is the primary determinant of the degree of pancreatic exocrine dysfunction. The presence of CFTR variants associated with severe pancreatic exocrine dysfunction is essentially a prerequisite for the development of diabetes and intestinal obstruction. In the setting of severe endocrine dysfunction, genetic modifiers determine when, and if, diabetes occurs and whether neonatal intestinal obstruction occurs.

The key histological features of ABPA include bronchocentric granulomas, eosinophilic pneumonia, and allergic mucin, which were classically missing in this case.

Absence of vas deferens is another feature often encountered and cause of male infertility.

SUGGESTED READING

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