PRESENTATION OF CASE (DR. MARICELA VALERIO)

A 60 year old lady, presented to the Emergency Department of Hospital General Universitario Gregorio Marañón (HGUOM) in Madrid in November 2017 with a 4 day history of malaise, fever, chest pain and dyspnea.

She had a left side breast cancer in 2001 that received treatment with surgical resection of the nodule, axillary lymphadenectomy, chemotherapy, local radiotherapy and finally, hormonal therapy with tamoxifen for 5 years and letrozol for 2 years. She had no recent evidence of recurrence.

She was a smoker until several years ago, when she quit smoking and did not report any drug allergy or to other products. She had no underlying heart disease and was not receiving, regularly, drugs of any kind. She had never travel out of Spain. She had not been vaccinated recently.

Six days before her admission she had a family touristic trip to an area in the North West of Spain called Las Médulas, an historical roman gold mining area in the province of León. She entered several caves and tunnels but denied any contact with animals or birds, including bats and no particular exposure to dust. She denied eating uncooked products or unpasturized milk or cheese.

During the trip, she started with fever, malaise and headache, and decided to prematurely return to Madrid and stayed at her home with symptomatic treatment, 4 days later she began with dry cough and dyspnea. Due to the rapid deterioration of her clinical condition she went to the Emergency Department (Day 0). On admission she had dyspnea, tachycardia and hypotension, blood cultures were obtained and IV fluids and antibiotic treatment with ceftriaxone (2 g IV q.d.) and levofloxacin (750 mg q.d.) was administered before her transfer to the Intensive Care Unit.

A chest X-ray taken on admission is shown in figure 1. Radiologic report states that “there is an Upper Right Lobe (URL) consolidation with potential amputation of the superior URL bronchus. Increased density in the right lung hilum. Possible pneumonia. A central hilum tumor should be ruled out”.

Other complementary data obtained on admission were the following: hemoglobin 12.7 g/dL, hematocrit value 35.9 %, mean corpuscular volume 93.2 fL, platelet count 170,000 uL, white blood count 6,800/uL (neutrophils 6,200 uL, lymphocytes 400 uL, monocytes 10 uL, eosinophils 300 uL). Prothrombin time 25.5 sec, I.N.R. 2.11, fibrinogen >1000 mg/dL, A.P.T.T. 35.8 sec.
Venous blood data: pH 7.43, pCO₂ 34 mmHg, pO₂ 28 mmHg, O₂ saturation of 55%, HCO₃ 23 mmol/L, BEb -1.2 mmol/L, lactate of 5.0 mmol/L, glucose 107 mg/dL, ALT 46 U/L, total bilirubin 1.2 mg/dL, GGT 19 U/L, alkaline phosphatase 49 U/L, CK 47 U/L, amilase 18 U/L, lipase 15 U/L, creatinine 1.03 mg/dL, glomerular filtrate 55 ml/min/1.73 m², Na 139 mmol/L, K 3.6 mmol/L, Cl 99 mmol/L, Ca 8.5 mg/dL, troponin T 6 ng/L, Nt-proBNP 5,204 ng/L, PCR 34.0 mg/dL, PCT 8.39 μg/L. Normal ECG.

ICU admission. Due to shock and progressive hypoxia (O₂ sat 91%) despite 100% ventimask and noradrenalin, she was transferred to the ICU. At the time of ICU admission she was conscious and mentally oriented with a Glasgow coma score of 15. The patient had sinus tachycardia. No heart murmurs were present. Abdomen was soft with no liver nor spleen enlargement. There was a discrete abdominal pain on palpation of the right hipocondrium. No signs of peritoneal irritation were present. No peripheral edema nor signs of deep venous thrombosis were present. Peripheral arteries pulsed symmetrically.

Legionella antigenuria was informed as negative and Streptococcus pneumoniae antigenuria as positive.

Day +2 after admission. A progressive deterioration of the respiratory function occurs and oro-tracheal intubation was required (Figure 2 Chest X ray). Persistent desaturation down to 75% occurred despite FiO₂ of 100% and PEEP of +18mmHg. Vasoactive drugs needs increased (adrenaline and noradrenaline) and a new right bundle block became evident in the urgently performed EKG. A trans-thoracic echocardiogram (TTE) revealed an important dilatation of the right ventricle with severely depressed function.

Day +3 to +6 after admission. An evolution to multi-organic failure occurred and blood cultures remained negative. Massive pulmonary thromboembolism was suspected and thrombolysis with alteplasa was performed. The patient required ECMO and continuous veno-venous hemofiltration (CVVHF) due to oliguric renal failure. On day +5 a fiberoptic bronchoscopy showed a permeable bronchial tree, with normal mucosa and no active bleeding. Samples for culture were obtained and antimicrobial treatment was modified, including now meropenem, vancomycin, and clindamycin.

A new TTE showed a severely dilated and severely dysfunctional right ventricle, with moderate-severe tricuspid valve dysfunction and a minimal pericardial fluid. Consumption coagulopathy persisted despite the administration of vitamin K and progressive anemia and thrombocytopenia develops. Cultures taken during fiber optic bronchoscopy were all negative.

Complementary data requested include: Negative AVH, BVH, CVH, VIH, Rose of Bengal, Rickettsia, Borrelia, Legionella, Mycoplasma, Coxiella, Chlamydia, Leptospira, Cryptococcal antigen and Aspergillus antigen.

Blood PCR for Bartonella and Coxiella burnetii were both negative. The Plasmodium antigen was also negative and no microorganisms were seen in Giemsa stains of peripheral blood samples. CMV and EBV viremia were negative.

Other negative respiratory samples included: RSV, Influenza A and B.

Day +7 after admission. An abdominal echocardiogram showed: Enlarged liver (Up to 19 cm) of homogenous parenchyma. Normal biliary tree. Spleen-portal axis and pancreas were unremarkable as were both kidneys and the excretory system. Minimal pleural fluid and ascitic fluid were detected. CT scan could not be performed due to the critical and unstable situation of the patient.

Final evolution. The patient died on day +10 of admission and a limited, echography guided autopsy, was authorized by the family.

DIFFERENTIAL DIAGNOSIS (DR. FRANCISCO LÓPEZ-MEDRANO)

Thank you very much for inviting me to discuss this clinical case. I am totally unaware of the final diagnosis of the case. Three important factors have to be considered for the final approach to the diagnosis of a potential infectious disease: the clinical manifestations and syndromic diagnosis, the time of evolution and the risk factors of the patient. Those three aspects for this patient are, in my opinion: pneumonia, of acute evolution after a visit to an historical, not active, mining roman area in Leon, Spain.

Regarding the first aspect, the patient is a 60 year old
lady, apparently immunocompetent, that develops a rapidly evolving febrile disease with pulmonary infiltrates and a positive urine test for pneumococcal antigen. Here we may have, in my opinion, three potential scenarios. First, we are assisting to an episode of fulminant pneumococcal pneumonia affecting an immunosuppressed patient, second, we have a false positive pneumococcal antigenuria and there is an alternative etiology for the pneumonia or, finally, this is an episode of pneumococcal pneumonia with co-infection with another microorganism. In a recent article by Sanges et al [1], patients 18 to 40 year-old who had experienced an invasive infection with encapsulated bacteria were examined searching for primary immunodeficiencies (PIDs). Out of 36 such cases, 7 (19%) had a PID which included idiopathic primary immunodeficiency and hypogammaglobulinemia and also complement (C6 and C7) deficiencies. Authors concluded that PID screening should be considered after a first unexplained invasive encapsulated-bacteria infection in young adults.

Regarding the issue of pneumococcal antigen present in this patient’s urine, Couturier et al [2] review the literature to that time and showed specificities of the test, generally from 90–100% with only occasional exceptions. My consideration is that this test is credible in this patient and very significant for my final diagnosis.

However, due to its fulminant course, we should consider other potentially treatable alternatives. We have to consider, either virus, bacteria, mycobacteria, fungi or parasites. Chapter 69 of the 2014 edition of Mandell’s textbook of Infectious Diseases, written by Ellison and Donowitz [3], lists in several tables, common and uncommon causes of acute pneumonia, but we have to try to reduce the size of this long list to maintain only those etiologies that best fit with the case from a clinical, radiological and epidemiological point of view. Influenza and Respiratory Syncytial Virus heads the list of common viral agents, S. pneumoniae is the main cause of bacterial infections and Histoplasma the most common cause of fungal pneumonia, particularly after visiting caves. When considering specifically the main causes of non-resolving pneumonia, Yersinia pestis, Burkholderia pseudomallei, Hantavirus sp., Coccidioides immitis, Blastomyces sp., Histoplasma sp. and Cryptococcus gattii are among the most commonly listed agents. Many of these agents are easily eliminated on the basis of epidemiological conditions and patient’s history. Cryptococcus gattii has been reported occasionally in Spain [4] and Strongyloides stercoralis has been also diagnosed in autochthonous Spanish populations (Valencia and Alicante, but not in León) [5]. Hantaviruses are the etiological agents of hemorrhagic fever with renal syndrome in Europe and Asia, and hantavirus pulmonary syndrome is mainly an American entity. There is seropositivity to Puuma la, Hantaan and Seoul virus only in a low proportion of persons in some regions of Spain [6, 7] but cases with pulmonary involvement have been never described in Spain and the diagnosis of Hantavirus is highly improbable in this lady. Regarding the area of the patients visit we were not able to find any suggestive entity compatible with this case even when Francisella tularensis was reported in vole populations in that part of Spain [8] and has been described in outbreaks in the past [9-12].

My final consideration is the possibility of having a pneumococcal pneumonia and “something else”.

In a review of the etiology of community-acquired pneumonia in the USA, reported by Jain et al [13], a bacterial and viral coinfection was demonstrated in 3% of the episodes. One virus of interest is adenovirus [14] that may occur in patients with no prior underlying condition. The same may occur with HSV in previously normal hosts that are able to cause a severe, non-resolving pneumonia in immunocompetent patients [15]. Bouza et al, reported Herpes simplex as a cause of worse prognosis when present in patients with ventilator-associated pneumonia [16].

**Dr. López Medrano Diagnosis**

My presumptive diagnosis is then: fulminant pneumococcal pneumonia due to co-infection with Herpes simplex virus or Adenovirus.

**EVOLUTION OF THIS PATIENT (DR. MARICELA VALEROI)**

In the final days of the life of the patient, or immediately after her death, the results of other requested tests were reported. Blood PCR test for Hantavirus and C. burnetii were reported negative and a blood test for Histoplasma spp. was also negative. Bacterial cultures of the bronchoalveolar lavage (BAL) samples were negative but a PCR test amplified S. pneumoniae. In the lung samples obtained by transthoracic biopsy after death, PCR was also positive for S. pneumoniae.

The liver and kidney echography guided biopsies obtained postmortem were negative by culture and PCR negative also.

Pathology reported changes compatible with disseminated intravascular coagulation. Bone marrow biopsy was

| Table 1 | Lymphocyte populations |
|---------|------------------------|
|         | Percentage | Normal range (%) | Absolute value (cells/µL) | Normal range (cells/µL) |
| T cells (CD3+) | 68% | 55-82 | 191 | 700-2100 |
| T cells (CD3+ CD4+) | 37% | 28-57 | 107 | 300-1400 |
| T cells (CD3+ CD8+) | 30% | 10-39 | 87 | 200-1200 |
| Coefficient CD4/CD8 | 1.2 | 1-3.6 | | |
| B cells (CD19+) | 24% | 6-19 | 65 | 100-500 |
| LGI/NK cells (CD3-/ CD56+) | 6% | 7-31 | 16 | 90-600 |
hypo-cellular with marked decrease of megakaryocytic and granulocytic series and a relative increase in the red blood cell series, with dyserythropoiesis. Findings were interpreted as compatible with sepsis, disseminated intravascular coagulation (DIC), and haemophagocytosis.

The Immunology Laboratory reported: anti-cardiolipin IgG and IgM, Anti-Beta 2 GPI IgG and IgM, native Anti-DNA and Anti-nuclear antibodies, all negative. Immuneprotein levels in serum were reported as follows: IgG 893.0 mg/dL (normal range: 650-1610), IgA 221.0 mg/dL (normal range 90-497), IgM 123.0 mg/dL (normal range 42-255). Other serum values included complement C3 57.7mg/dL (normal range 91-190), C4 14.4mg/dL (normal range 18-56) and C-reactive protein 18.4mg/dL (normal range 0-0.8). Figures of different lymphocytic populations were clearly decreased and are summarized in table 1.

FINAL DISCUSSION

Several points of the presentation and evolution of this case deserve discussion, in our opinion.

First of all, the patient had, among the early laboratory tests, a positive pneumococcal antigen in urine. Determination of pneumococcal antigen in urine, is recommended by IDSA in patients with pneumonia that require ICU admission, those who fail response to the initial antibiotic treatment, patients with low white blood count, alcoholics and patients with pleural effusion and asplenia [17]. Sensitivity and specificity of this test vary depending on different circumstances. Blaschke et al reported [18], sensitivities with the Binax NOW test from 70 to 90 % with specificities from 80 to 100% in adults with pneumonia. Results may be worse in patients who are nasopharyngeal carriers of *S. pneumoniae* and better in patients with severe infection and bacteremic pneumococcal pneumonia [19-21].

Another question in this case, is the interpretation of a specific PCR for *S. pneumoniae*, both in lower respiratory tract samples obtained by BAL and in lung biopsies postmortem. Sensitivity is considered variable but specificity could be superior to 95% according to different authors [22-25].

The reasons for the very aggressive behavior of pneumococcal infection in this patient, remain obscure for us. Fulminating pneumococcal infection is an uncommon but well known situation, particularly in immunocompromised and asplenic patients, either traumatic or functional [26-37]. However, it can also occur in non-immunocompromised subjects by mechanisms that are not totally clarified [38]. We could not demonstrate a situation of functional asplenia in our patient and only speculated with the potential radiation of the spleen while she received radiotherapy for her left breast cancer, several years before.

This patient, had very low figures of serum complement, that have also been associated with a risk of poor evolution in patients with pneumococcal infection [39-43]. Hypocomplementemia may be in the origin of the evolution of this patient, but in our opinion, it is the consequence of sepsis and DIC [44].

A previous report suggested that pneumococcal capsular polysaccharides (PCPs) were responsible for initiating DIC through inflammation induced by PCPs, per se, or an antigen–antibody reaction [45]. Also, certain serotypes of *S. pneumoniae* may be particularly invasive [46] but not having an isolate, we were unable to serotype this case.

Another probable diagnosis that needs to be mentioned, is the hemophagocytic syndrome secondary to the infection. The most common infectious trigger of this syndrome are viral infections. Bacterial causes are less common but cases of *S. pneumoniae* infection related hemophagocytic syndrome have been described [47, 48]. Hemophagocytic syndrome could be diagnosed if at least 5 out of 8 criteria are present, our patient only met 4 of them (fever, hypofibrinogenemia, hemophagocytosis and bicitopenia) but ferritin concentrations, CD25 levels and cytotoxic activity of NK cells were not determined [49].

Finally, we were surprised by the severe cardiovascular events of this patient. It is known that patients hospitalized for pneumococcal pneumonia have a higher risk of cardiovascular events than similar populations. Complications include, acute myocardial infarction, auricular fibrillation, ventricular tachycardia and acute heart failure [50-54]. Most commonly, those events occur very early in the natural history of pneumococcal infection with 55% of them reported in the very first day of admission, with a progressive decrease in the following month. Musher et al [55] found 33 cardiovascular severe events in a population of 170 cases admitted with pneumococcal pneumonia. A national retrospective cohort of patients with pneumococcal pneumonia in Taiwan was compared with a similar population without pneumonia, and the authors showed a higher risk of thromboembolic episodes [deep venous thrombosis and pulmonary embolisms] in the population with pneumonia, particularly within the first four weeks of evolution [56].

This patient had never received a pneumococcal vaccine, and our speculation in the discussion of the case was if vaccination could have avoided this episode or at least decreased its severity and preserve patient’s life.

FINAL DIAGNOSIS

Invasive pneumococcal infection with pneumonia and fulminant sepsis.

Disseminated intravascular coagulation.

Right heart failure probably due to pulmonary embolism.

Hypocomplementemia and lymphopenia

FUNDING

None to declare.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.
REFERENCES

1. Sanges S, Wallet F, Blondiaux N, Theis D, Verin J, Vachee A, et al. Diagnosis of primary antibody and complement deficiencies in young adults after a first invasive bacterial infection. Clin Microb Infect. 2017 Aug;23(8):576.e1-e5. PubMed PMID: 28192236.

2. Couturier MR, Graf EH, Griffin AT. Urine antigen tests for the diagnosis of respiratory infections: legionellosis, histoplasmosis, pneumococcal pneumonia. Clin Lab Med. 2014 Jun;34(2):219-36. PubMed PMID: 24856525.

3. Ellison RT III, OR D. Acute Pneumonia. In: Bennett JE, Dolin R, Blaser MJ, ed. Mandell, Douglas and Bennett’s Principles and Practice of Infectious Diseases, 8th edition, Philadelphia, PA; Churchill Livingstone Elsevier. 2014.

4. Colom MF, Frases S, Ferrer C, Jover A, Andreu M, Reus S, et al. First case of human cryptococcosis due to Cryptococcus neoformans var. gattii in Spain. J Clin Microbiol. 2005 Jul;43(7):3548-50. PubMed PMID: 16000503.

5. Pacheco-Tenza MI, Ruiz-Macia JA, Navarro-Cots M, Gregori-Colome J, Cepeda-Rodrigo JM, Llanas-Garcia J. Strongyloides stercoralis infection in a Spanish regional hospital: Not just an imported disease. Enferm Infecc Microbiol Clin. 2018 Jan;36(1):24-8. PubMed PMID: 27743682.

6. Sanfeliu I, Nogueras MM, Gentzsch MI, Segura F, Lledo L, Font B, et al. Seroepidemiological survey of hantavirus infection in healthy people in Valles Occidental, Barcelona. Vector Borne Zoonotic Dis. 2011 Jun;11(6):697-700. PubMed PMID: 21417923.

7. Lledo L, Gentzsch MI, Ledesma J, Domingo C, Gonzalez R, Romanyk J, et al. Prevalence of anti-hantavirus antibodies in patients with hypertransaminemia in Madrid (Spain). Am J Trop Med Hyg. 2007 Aug;77(2):371-5. PubMed PMID: 17690415.

8. Rodriquez-Pastor R, Escudero R, Vidal D, Mougeot F, Arroyo B, Lambin X, et al. Density-Dependent Prevalence of Francisella tularensis in Fluctuating Vole Populations, Northwestern Spain. Emerg Infect Dis. 2017 Jul;23(7):1377-9. PubMed PMID: 28726608.

9. Bachiller Luque P, Perez Castrillon JL, Martin Luquero M, Mena Martin FJ, de la Lama Lopez-Areal J, Perez Pascual P, et al. [Preliminary report of an epidemic tularemia outbreak in Valladolid]. Rev Clin Esp. 1998 Dec;198(12):789-93. PubMed PMID: 9929997.

10. Barabote RD, Xie G, Brettin TS, Hinrichs SH, Fey PD, Jay JJ, et al. Complete genome sequence of Francisella tularensis subspecies holarctica FTN002-00. PLoS One. 2009 Sep 16;4(9):e7041. PubMed PMID: 19756146.

11. Belhassen-Garcia M, Velasco-Tirado V, Alvella-Suarez L, Fraile-Alonso Mdcl C, Carpio-Peraz A, Pardo-Lledias J. Cavitary pneumonia and skin lesions. Respir Care. 2012 Mar;57(3):457-9. PubMed PMID: 22005344.

12. Bellido-Casado J, Perez-Castrillon JL, Bachiller-Luque P, Martin-Luquero M, Mena-Martin FJ, Herreos-Fernandez V. Report on five cases of tularemia pneumonia in a tularemia outbreak in Spain. Eur J Clin Microbiol Infect Dis. 2000 Mar;19(3):218-20. PubMed PMID: 10795596.

13. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N Engl J Med. 2015 Jul 30;373(5):415-27. PubMed PMID: 26172429.

14. Low SY, Tan TT, Lee CH, Loo CM, Chew HC. Severe adenovirus pneumonia requiring extracorporeal membrane oxygenation support--Serotype 7 revisited. Respir Med. 2013 Nov;107(11):1810-3. PubMed PMID: 24070567.

15. Hunt DP, Muse W, Pitman MB. Case records of the Massachusetts General Hospital. Case 12-2013. An 18-year-old woman with pulmonary infiltrates and respiratory failure. N Engl J Med. 2013 Apr 18;368(16):1537-45. PubMed PMID: 23594007.

16. Bouza E, Giannella M, Torres MV, Catalan P, Sanchez-Carrillo C, Hernandez RI, et al. Herpes simplex virus: a marker of severity in bacterial ventilator-associated pneumonia. J Crit Care. 2011 Aug;26(4):432.e1-6. PubMed PMID: 21129912.

17. Mandell LA, Wunderink RG, Anzueto A. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2:S1-27. PubMed PMID: 17278083.

18. Blaschke AJ. Interpreting assays for the detection of Streptococcus pneumoniae. Clin Infect Dis. 2011 May;52 Suppl 4:S331-7. PubMed PMID: 21460292.

19. Gutierrez F, Masia M, Rodriguez JC, Ayelo A, Soldan B, Cebrian L, et al. Evaluation of the immunochromatographic Binax NOW assay for detection of Streptococcus pneumoniae urinary antigen in a prospective study of community-acquired pneumonia in Spain. Clin Infect Dis. 2003 Feb 1;36(3):286-92. PubMed PMID: 12539069.

20. Roson B, Fernandez-Sabe N, Carratala J, Verduguer R, Dorca J, Manresa F, et al. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis. 2004 Jan 15;38(2):222-6. PubMed PMID: 14699454.

21. Sorde R, Falco V, Lowak M, Domingo E, Ferrer A, Burgos J, et al. Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy. Arch Intern Med. 2011 Jan 24;171(2):166-72. PubMed PMID: 20876397.

22. Sanz JC, Rios E, Rodriguez-Aival J, Ramos B, Marin M, Cercenado E. Identification of Streptococcus pneumoniae lytA, plyA and psaA genes in pleural fluid by multiplex real-time PCR. Enferm Infecc Microbiol Clin. 2017 Aug 14. PubMed PMID: 28818481.

23. Gillis HD, Lang ALS, ESherif M, Martin I, Hatchette TF, McNeil SA, et al. Assessing the diagnostic accuracy of PCR-based detection of Streptococcus pneumoniae from nasopharyngeal swabs collected for viral studies in Canadian adults hospitalised with community-acquired pneumonia: a Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research (CIRN) study. BMJ Open. 2017 Jun 8;7(6):e015008. PubMed PMID: 28600368.

24. Blake A, Njanpop-Lafourcade BM, Telles JN, Rajoharison A, Makawa MS, Aghenoko K, et al. Evaluation of chest radiography, lytA real-time PCR, and other routine tests for diagnosis of community-acquired pneumonia and estimation of possible attributable fraction of pneumococcus in northern Togo. Epidemiol Infect. 2017 Feb;145(3):583-94. PubMed PMID: 27852346.
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25. Habets MN, Cremers AJ, Bos MP, Savelkouli P, Eleveld MJ, Meis JF, et al. A novel quantitative PCR assay for the detection of Streptococcus pneumoniae using the competence regulator gene target comX. J Med Microbiol. 2016 Feb;65(2):129-36. PubMed PMID: 26628261.

26. Lijsma S. Sporadic isolated congenital asplenia with fulminant pneumococcal meningitis: a case report and updated literature review. BMC Infect Dis. 2017 Dec 18;17(1):777. PubMed PMID: 29254492.

27. Hale AJ, LaSalvia M, Kirby JE, Kimball A, Baden R. Fatal purpura fulminans and Waterhouse-Friderichsen syndrome from fulminant Streptococcus pneumoniae sepsis in an asplenic young adult. ID Cases. 2016;6:1-4. PubMed PMID: 27583208.

28. White C, Guarascio AJ, Draper HM. Fatal purpura fulminans and septic shock in asplenic patient with Streptococcus pneumoniae bacteremia. J Am Pharm Assoc. 2014 Jan-Feb;54(1):88-90. PubMed PMID: 24407746.

29. Konda S, Zell D, Mlikowski C, Alonso-Llamazares J. Purpura fulminans associated with Streptococcus pneumoniae septicemia in an asplenic pediatric patient. Actas Dermo-sifiliogr. 2013 Sep;104(7):623-7. PubMed PMID: 23985086.

30. Nohynek H. Protecting asplenic individuals from fulminant pneumococcal disease. Euro Surveill. 2010 Jun 10;15(23). PubMed PMID: 20546696.

31. Chironna M, Sallustio A, De Robertis A, Quarto M, Germinario C. A novel quantitative PCR assay for the detection of Streptococcus pneumonia and the cardiovascular system. Lancet. 2013 Feb;381(9865):496-505. PubMed PMID: 23332146.

32. Pancharoen C, Chatchatee P, Ngamphaiboon J, Thisyakorn U. Role of Complement C1q in Pneumococcal disease. Euro Surveill. 2010 Jun 10;15(23). PubMed PMID: 20546696.

33. Zimmerli W, Schaffner A, Scheidegger C, Scherz R, Spath PI. Humoral immune response to pneumococcal antigen 23-F in an asplenic patient. J Infect Dis. 1991 Jan;162(1):59-68. PubMed PMID: 2002233.

34. Rusonis PA, Robinson HN, Lamberg SI. Livedo reticularis and purpura: presenting features in fulminant pneumococcal septicemia in an asplenic patient. J Am Acad Dermatol. 1986 Nov;15(5 Pt 2):1120-2. PubMed PMID: 3771863.

35. Bourgault AM, Van Scoy RE, Wilkowske CJ, Sterioff S. Severe infection due to Streptococcus pneumoniae in asplenic renal transplant patients. Mayo Clin Proc. 1979 Feb;54(2):123-6. PubMed PMID: 3868440.

36. Latos DL, Stone WJ. Fulminant pneumococcal bacteremia in an asplenic chronic hemodialysis patient. Johns Hopkins Med J. 1978 Nov;143(5):165-8. PubMed PMID: 31505.

37. Gopal V, Bisno AL. Fulminant pneumococcal infections in 'normal' asplenic hosts. Arch Intern Med. 1977 Nov;137(11):1526-30. PubMed PMID: 921438.

38. Naito R, Miyazaki T, Kajino K, Daida H. Fulminant pneumococcal infection. BMJ Case Rep. 2014 Aug 22;2014. PubMed PMID: 25150240.

39. Andre GO, Converso TR, Polizano WR, Ferraz LF, Ribeiro ML, Leite LC, et al. Role of Streptococcus pneumoniae Proteins in Evasion of Complement-Mediated Immunity. Front Microbiol. 2017;8:224. PubMed PMID: 28265264.

40. Agarwal V, Blom AM. Roles of Complement C1q in Pneumococcus-Host Interactions. Crit Rev Immunol. 2015;35(3):173-84. PubMed PMID: 26559226.

41. Ruiz S, Segonds C, Georges B, Puissant B, Ponard D, Fourcade O, et al. [Fulminant pneumococcosis: bacteria and complement partners in crime]. Ann Fr Anesth Reanim. 2010 Jul-Aug;29(7-8):593-4. PubMed PMID: 20598496.

42. Mold C, Rodic-Polic B, Du Clos TW. Protection from Streptococcus pneumoniae infection by C-reactive protein and natural antibody requires complement but not Fc gamma receptors. J Immunol. 2002 Jun 15;168(12):6375-81. PubMed PMID: 12055255.

43. Winkelstein JA. The role of complement in the host's defense against Streptococcus pneumoniae. Rev Infect Dis. 1981 Mar-Apr;3(2):289-98. PubMed PMID: 7020046.

44. Gilbert RD, Nagra A, Haq MR. Does dysregulated complement activation contribute to haemolytic uraemic syndrome secondary to Streptococcus pneumoniae? Med Hypotheses. 2013 Sep;81(3):400-3. PubMed PMID: 23786906.

45. Rytel MW, Dee TH, Ferstenfeld JE, Hensley GT. Possible pathogenic role of capsular antigens in fulminant pneumococcal disease with disseminated intravascular coagulation (DIC). Am J Med. 1974 Dec;57(6):889-96. PubMed PMID: 4139894.

46. Brueggemann AB, Peto TE, Crook DW, Butler JC, Kristinsson KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. J Infect Dis. 2004 Oct 1;190(7):1203-11. PubMed PMID: 15346329.

47. Dumancas CY, Reyes HAG, Cosico J, Savadkar A, Lah S. Streptococcus pneumoniae-Related Hemophagocytic Lymphohistiocytosis Treated with IVIG and Steroids. Am J Case Rep. 2018 Jan 8;19:25-8. PubMed PMID: 29307884.

48. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014 Apr;4(8):29-39. PubMed PMID: 2490661.

49. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. J Infect Dis. 2004 Oct 1;190(7):1203-11. PubMed PMID: 15346329.

50. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. J Infect Dis. 2004 Oct 1;190(7):1203-11. PubMed PMID: 15346329.

51. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. J Infect Dis. 2004 Oct 1;190(7):1203-11. PubMed PMID: 15346329.

52. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. J Infect Dis. 2004 Oct 1;190(7):1203-11. PubMed PMID: 15346329.

53. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. J Infect Dis. 2004 Oct 1;190(7):1203-11. PubMed PMID: 15346329.

54. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of Streptococcus pneumoniae in children. J Infect Dis. 2004 Oct 1;190(7):1203-11. PubMed PMID: 15346329.
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