CASE REPORT

Pneumococcal vaccine failure: Can it be a primary immunodeficiency?

Rita Moinho,¹ Ana Brett,¹ Gisela Ferreira,² Sónia Lemos¹¹Hospital Pediátrico de Coimbra, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal²Department of Serviço de Hematologia, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal**Correspondence to**
Dr Rita Moinho,
Ritamoinho@gmail.com

Accepted 25 May 2014

SUMMARY

Vaccine failure is a rare condition and the need to investigate a primary immunodeficiency is controversial. We present the case of a 4-year-old boy, with complete antipneumococcal vaccination, who had necrotising pneumonia with pleural effusion and severe pancytopenia with need for transfusion. A vaccine-serotype *Streptococcus pneumoniae* was isolated in the blood culture. On follow-up, detailed medical history, laboratory and genetic investigation led to the diagnosis of X linked dyskeratosis congenita. Dyskeratosis congenita is an inherited disorder that causes shortening or dysfunction of telomeres, affecting mainly rapidly dividing cells (particularly in the skin and haematopoietic system). It leads to bone marrow failure, combined immunodeficiency and predisposition to cancer. The confirmation of this diagnosis allows genetic counselling and medical monitoring of these patients, in order to detect early complications such as bone marrow aplasia or malignancies.

BACKGROUND

Vaccine efficacy is widely recognised. However, a few vaccine failure cases can be expected as vaccines are generally not 100% effective.^{1 2}

Since the implementation of the pneumococcal conjugate vaccine (PCV), several studies have demonstrated vaccine-type PCV efficacy against invasive pneumococcal disease (IPD) of around 90–96% in fully vaccinated healthy children.^{1 3–5} The immune response to PCV varies according to the number of doses administered and the different serotypes, which are not equally immunogenic.^{1 6} An incomplete vaccination schedule has been identified as a risk factor for PCV failure, particularly for serotypes 6B and 19F.¹ Also, immunodeficiencies and other chronic diseases increase the risk of IPD and PCV failure.^{1 5 7} Nevertheless, most IPD cases by vaccine failure occur in children whose investigation revealed no underlying disease.¹

We present the case of a 4-year-old boy with vaccine-serotype IPD and pancytopenia, who was later diagnosed with X linked dyskeratosis congenita (DC).

Our aim is to illustrate the importance of a thorough clinical history and examination, as well as appropriate laboratory investigation, when assessing a case of vaccine failure.

CASE PRESENTATION

A 4-year-old boy was admitted to the emergency service of his local hospital with a 6-day history of fever, slight cough, dyspnoea and thoracic pain in

the last 2 days. He had been treated with amoxicillin (90 mg/kg/day) for 2 days with no evident improvement. His chest X-ray showed a right lobar pneumonia and his blood tests showed pancytopenia (haemoglobin 9.1 g/dL, leucocytes 3600/μL and platelets 18 000/μL). He was started on ceftriaxone and vancomycin.

After admission, his clinical status deteriorated with haematemesis, and he was transferred to the paediatric intensive care unit of a tertiary centre. On admission, he was pale and had multiple facial and oral mucosa petechiae; breath sounds were diminished in the lower two-thirds of his right lung. Blood tests showed worsening pancytopenia (haemoglobin 7.9 g/dL, leucocytes 5110/μL with 3520/μL neutrophils and 1160/μL lymphocytes and platelets 8000/μL), elevated C reactive protein (340 mg/L) and procalcitonin (15 ng/mL). Chest X-ray and chest CT showed right necrotising pneumonia with extensive biloculated pleural effusion (figures 1 and 2).

He improved slowly, with persistently high fevers up to the 10th day of admission. He needed platelet, plasma and red blood cell transfusion. *Streptococcus pneumoniae* was isolated from the blood culture, sensitive to all tested antibiotics. Serotyping was performed by the standard capsular reaction test using the chessboard system and specific sera (Statens Serum Institute, Copenhagen, Denmark), and serotype 14 was detected. He was

Figure 1 Chest X-ray showing a right pneumonia with pleural effusion.

CrossMark

To cite: Moinho R, Brett A, Ferreira G, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-204714

Figure 2 Chest CT showing necrotising pneumonia with pleural effusion.

fully vaccinated according to the national vaccination programme, as well as three doses of PCV-7 (3, 5 and 6 months of age) and one dose of PCV-13 (18 months). There was no growth from his pleural effusion. He was treated 14 days with vancomycin and 10 days with ceftriaxone, replaced by penicillin for another 2 weeks. After 1 month of admission he was discharged home, clinically well.

During the following months he was assessed in the respiratory medicine clinic and the immunodeficiency clinic of the tertiary paediatric centre. He was clinically well, with no symptoms, but blood tests showed persistent thrombocytopaenia.

He was a first-born, with the pregnancy complicated by intra-uterine growth restriction in the last trimester. Birth was at 35 weeks gestational age, with good adaptation to extrauterine life. His birth weight was 1760 g, appropriate for his gestational age. Growth and development the following years were normal.

He had had right paracardiac pneumonia when he was 3 years old and several episodes of tonsillitis.

His parents are non-consanguineous and healthy. He has a first-degree cousin from his mother's side, currently 16 years old, with osteosarcoma and his maternal grandfather died from pancreatic cancer.

On physical examination he had thin and easily breakable hair, his skin had an overall reticulated pattern and he had dystrophic nails on his feet. He also presented with oral leukoplakia and multiple dental caries (figure 3). The remaining examination was normal.

INVESTIGATIONS

Initial assessment for primary immunodeficiency showed: thrombocytopaenia (57 000/ μ L), low IgM 0.34 g/L (normal

values 0.47–2.00), low CD19 3% (normal values 16–24%) and CD4/CD8 in V.0.72 (normal values 1.3–2.1). IgG subclasses and complement were normal.

Given his clinical history and abnormal physical examination, as well as the changes in his blood workup, a bone marrow exam was performed that showed normal/hypocellular fragments with erythroid dysplasia.

DC was hypothesised and DNA extraction for genetic study was performed, which showed haemizygosity to a known mutation of the DKC1 gene (c200C>T), confirming the diagnosis of X linked DC.

OUTCOME AND FOLLOW-UP

Currently on follow-up, he remains clinically stable. He was started on prophylaxis with cotrimoxazole and a genetic study of the maternal family is planned.

DISCUSSION

Most cases of IPD in PCV vaccinated children are by non-vaccine serotypes and rare cases of true vaccine failure have been reported.^{1 6 8} Serotype 14, isolated in this clinical case, is included in both PCV-7 and PCV-13 and studies report a $\geq 97\%$ coverage rate for this serotype when four doses are administered.⁹

A surveillance study after implementation of PCV-7 in the USA, showed that 4% of IPD cases were due to vaccine failure of which 37% were associated with a comorbidity, in 13% a primary or acquired immunodeficiency.¹ A similar study in the UK reported a 3.9% rate of vaccine failure with PCV-7 of which 29% had an underlying illness.⁸ In this clinical case, vaccine failure, leukoplakia, dystrophic nails, reticulated skin and thrombocytopaenia as well as a family history of cancer presented with clues that led to the diagnosis of DC.

DC is a rare hereditary telomerase disorder, with most cases X linked and an estimated incidence of 1:1 000 000.^{10–16} It affects rapidly dividing tissues, often leading to bone marrow failure with associated immunodeficiency.^{10 11}

In this case, the genetic study demonstrated a mutation in the DKC1 gene (c200C>T), located on chromosome Xq28, already described once,¹⁷ confirming an X linked form of DC. The gene encodes the dyskerin protein, which has an important role in the biogenesis of ribosomes and in the function of RNA telomerase, involved in the maintenance of telomere length.^{11 18–23} Heterozygous females with DKC1 mutations can show highly penetrant telomere phenotypes.¹⁵ There are also autosomal dominant and autosomal recessive forms of DC.^{11–13 14 17–19 21 22 24–26}

When telomeres become critically short, cell apoptosis is activated with premature cell aging.^{19 21 24} Also, an increase of

Figure 3 On the left, nail dystrophy on the patient's feet, and on the right oral leukoplakia lesions.

reactive oxygen species occurs, which may have a bearing on DC pathogenesis.¹⁶ In patients with DKC1 mutation, clinical presentation tends to be more severe, with mucocutaneous changes occurring prior to bone marrow failure,^{18 25} as was observed in this case.

An anticipation phenomenon occurs, with progressively more severe forms of the disease in successive generations, probably due to progressive shortening of telomeres.^{19 21} This might have happened in this family, the child's maternal grandfather possibly had the same disease.

The classic disease triad, present in about 90% of DC cases, includes nail dystrophy, mucosal leukoplakia and changes in skin pigmentation.^{10–14 17–22 24 25 27} These clinical features are not usually present at birth, but often appear in childhood, with a variable age at diagnosis (median 15 years, range 0–75 years).^{10 13 18 25} Skin pigmentation abnormalities and nail dystrophy usually appear before the age of 10 and mucosa leukoplakia most typically begins in the second decade of life, with reported cases of black pigmentation on the leukoplakia lesion.^{13 14 18 19 22 25 27} In this case, the triad was present already at 4 years of age. The earlier the disease manifests, the greater the clinical severity,²¹ leading to predict poor prognosis.

A wide spectrum of disorders can be seen in DC, potentially affecting every system of the body.^{13 22} Other DC manifestations are pulmonary and hepatic fibrosis, with portal hypertension, cerebellar hypoplasia and atresia of the lacrimal ducts.^{26 27} In the present case, other features can be explained by the disease, such as intrauterine growth restriction in pregnancy, thin hair and dental caries.^{12 18–21 23–25}

The most frequent causes of mortality and major complications are bone marrow failure/immunodeficiency (60–70%), pulmonary complications (10–15%) and malignancy (10%).^{10–13 18 24 25 27} Bone marrow failure usually develops before the age of 20.^{12 14 18 22 24} Initially a single lineage may be involved, most often with isolated thrombocytopaenia (as was seen in this case) and later the remaining lineages are involved, progressing into severe bone marrow failure.^{12 18} Immunodeficiency in DC can lead to severe infection and be the first manifestation of the disease in childhood,^{10 13} as in this case. Humoral and cellular immune defects are common, which may condition serious and potentially fatal infections early in life.^{10 13} In particular, these patients have a defective T-cell antigen-specific proliferation, as memory T lymphocytes undergo greater antigen induced clonal expansion than naïve T lymphocytes, resulting in shorter telomeres. This leads to premature senescence of memory T cells and resultant impaired proliferation to antigen re-exposure.¹⁰

Multidisciplinary medical care is advisable (paediatrician, haematologist, dentist and geneticist). The only definitive treatment is haematopoietic cell transplantation, indicated when pancytopenia does not improve under medical therapy.^{11 14 18 20 22 25} Depending on the immune status, intravenous immunoglobulin and cotrimoxazole prophylaxis should be considered.¹⁰ Identification of mutations is crucial for genetic counselling. In this case, a study of the maternal family is planned.

Regular follow-up of these patients will lead to the early detection of frequent complications such as bone marrow failure and malignant complications and may allow for curative treatment.

In cases of vaccine failure, it is important for the paediatrician to document a detailed medical history and carry out a careful physical examination to identify possible signs that evoke an underlying immunodeficiency.

Learning points

- ▶ Vaccine failure is a rare condition that can be a sign of an underlying disease.
- ▶ In cases of vaccine failure, the paediatrician has an important role in recognising signs of an underlying disease from the medical history and physical examination.
- ▶ The first manifestations of dyskeratosis congenita (DC) often occur in childhood (including nail dystrophy and changes in skin pigmentation).
- ▶ DC is a multisystemic disease and immunodeficiency is a frequent complication with significant morbidity and mortality.

Acknowledgements The authors would like to thank Dra Manuela Benedito Professor Tom Vulliamy.

Contributors RM developed the idea for the article, collected clinical data, performed the literature search and wrote the article. AB carried out the literature search, helped to collect clinical data and wrote the article. GF was involved in critical revision of the manuscript. SL managed the patient and was involved in critical revision of the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Park SY, Van Beneden CA, Pilishvili T, *et al.* Invasive pneumococcal infections among vaccinated children in the United States. *J Pediatr* 2010;156:478–83.
- 2 Centers for Disease Control and Prevention. General Recommendations on Immunization of the Advisory Committee on Immunization Practices and the American Academy of Family Physicians. *MMWR Morb Mortal Wkly Rep* 2002;51:1–2.
- 3 Black S, Shinefield H, Fireman B, *et al.* Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J* 2000;19:187–95.
- 4 Whitney CG, Pilishvili T, Farley MM, *et al.* Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. *Lancet* 2006;368:1495–502.
- 5 Braidot F, Bellotti M, De Maria A, *et al.* The role of pneumococcal vaccine. *Pulm Pharmacol Ther* 2008;21:608–15.
- 6 Harboe ZB, Valentiner-Branth P, Ingels H, *et al.* Pediatric invasive pneumococcal disease caused by vaccine serotypes following the introduction of conjugate vaccination in Denmark. *PLoS ONE* 2013;8:e51460.
- 7 Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine. *MMWR Morb Mortal Wkly Rep* 2010;59:1–15.
- 8 Ladhani SN, Slack MPE, Andrews NJ, *et al.* Invasive pneumococcal disease after routine pneumococcal conjugate vaccination in children, England and Wales. *Emerg Infect Dis* 2013;19:61–8.
- 9 Bryant KA, Block SL, Baker SA, *et al.* Safety and immunogenicity of a 13-valent pneumococcal conjugate vaccine. *Pediatrics* 2010;125:866–75.
- 10 Jyonouchi S, Forbes L, Ruchelli E, *et al.* Dyskeratosis congenita: a combined immunodeficiency with broad clinical spectrum—a single center pediatric experience. *Pediatr Allergy Immunol* 2011;22:313–19.
- 11 Antunes MB, Gonçalves C, Vale MJ, *et al.* Disqueratose congénita, uma doença enigmática. *Nascer e Crescer* 2008;17:80–2.
- 12 Baran I, Nalcaci R, Kocak M. Dyskeratosis congenita: clinical report and review of the literature. *Int J Dent Hygiene* 2010;8:68–74.
- 13 Carvalho SP, Pereira LB, Silva CMR, *et al.* Disqueratose congénita—relato de caso e revisão da literatura. *An Bras Dermatol* 2003;78:579–86.
- 14 Nishio N, Kojima S. Recent progress in dyskeratosis congenita. *Int J Hematol* 2010;92:419–24.
- 15 Alder JK, Parry EM, Yegnasubramanian S, *et al.* Telomere phenotypes in females with heterozygous mutations in the dyskeratosis congenita 1 (DKC1) gene. *Hum Mutat* 2013;34:1481–5.

- 16 Pereboeva L, Westin E, Patel T, *et al*. DNA damage responses and oxidative stress in dyskeratosis congenita. *PLoS ONE* 2013;8:e76473.
- 17 Vulliamy T, Marrone A, Knight SW, *et al*. Mutations in dyskeratosis congenita: their impact on telomere length and the diversity of clinical presentation. *Blood* 2006;107:2680–5.
- 18 Dokal I. Dyskeratosis congenita. *Hematol Am Soc Hematol Educ Program* 2011;2011:480–6.
- 19 Kirwan M, Dokal I. Dyskeratosis congenita, stem cells and telomeres. *Biochim Biophys Acta* 2009;1792:371–9.
- 20 Savage S, Dokal I, Armanios M, *et al*. Dyskeratosis congenita: the first NIH clinical research workshop. *Pediatr Blood Cancer* 2009;53:520–3.
- 21 Bessler M, Wilson DB, Mason PJ. Dyskeratosis congenita. *FEBS Lett* 2010;584:3831–8.
- 22 Walne AJ, Dokal I. Advances in the understanding of dyskeratosis congenita. *Br J Haematol* 2009;145:164–72.
- 23 Safa WF, Lestringat GG, Frossard PM. X-linked dyskeratosis congenita: restrictive pulmonary disease and a novel mutation. *Thorax* 2001;56:891–4.
- 24 Nelson ND, Betuch AA. Dyskeratosis congenital as a disorder of telomere maintenance. *Mutat Res* 2012;730:43–51.
- 25 Dokal I, Vulliamy T. Dyskeratosis congenital: its link to telomerase and aplastic anemia. *Blood Rev* 2003;17:217–25.
- 26 Yoshida H, Imamura T, Sakamoto K, *et al*. Dyskeratosis congenita complicated by hepatic fibrosis. *J Pediatr Hematol Oncol* 2013;36:208–11.
- 27 Karunakaran A, Ravindran R, Arshad M, *et al*. Dyskeratosis congenita: a report of two cases. *Case Rep Dent* 2013;2013:845125.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow