Isolated cytokine-enriched pericardial effusion: A likely key feature for Aymé-Gripp syndrome

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Abstract
Aymé-Gripp syndrome is a multisystem disorder caused by a heterozygous variation in the MAF gene (OMIM*177075). Key features are congenital cataracts, sensorineural hearing loss, and a characteristic facial appearance. In a proportion of individuals, pericardial effusion or pericarditis has been reported as part of the phenotypic spectrum. In the present case, a large persistent cytokine-enriched pericardial effusion was the main pre- and postnatal symptom that led to the clinical and later molecular diagnosis of Aymé-Gripp syndrome. We propose that activating dominant variants in the cytokine-modulating transcription factor c-MAF causes cytokine-enriched pericardial effusions possibly representing a key feature of Aymé-Gripp syndrome.

KEYWORDS
Aymé-Gripp syndrome, congenital cataract, hearing loss, pericardial effusion

1 | INTRODUCTION

Aymé-Gripp syndrome is a multisystem disorder caused by monoallelic variants within the transactivation domain of the v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog (MAF). Disease-causing variants in the MAF lead to a clinical picture comprising sensorineural hearing loss, early onset cataracts, and characteristic facial features originally described as Down syndrome-like, and in a considerable number of cases, pericardial effusion. Furthermore, the syndrome is associated with developmental delay along with non-specific brain malformations and seizures of varying degree and severity (Niceta et al., 2015). So far 21 individuals have been reported in the literature. Here we describe a case in which pre- and postnatal cytokine-enriched pericardial effusion has been the key feature leading to the clinical and later molecular diagnoses of Aymé-Gripp syndrome.

2 | CASE REPORT

The boy was born by spontaneous vaginal delivery at 38+4 weeks of gestation with a previous history of a large pericardial effusion measuring 8–10 mm, first detected on fetal ultrasound at 33+4 weeks of gestation. The pericardial effusion was closely monitored during pregnancy, showing only slight increase to a maximum of 14–15 mm. Doppler measurements as well as M-mode ultrasound always showed...
good cardiac function despite the large fluid collection. Due to eventually compromising cardiac output, pericardiocentesis was performed the day before delivery. Biochemical analysis of the fluid did not show any signs of infection or malignancy. Also, all testing for maternal infection that could lead to fetal pericardial effusion came negative. Further prenatal scans with the first at 22+0 weeks of gestation showed normal fetal development. A very slight retroglossia was noted at 37+5 weeks of gestation, otherwise there were no signs of any structural or functional abnormalities especially none associated with pericardial effusions.

His birth weight was 3180 g (30th centile), his length was 50 cm (25th centile), and his head circumference was 35 cm (50th centile). At 4 min of life, pediatric intervention with non-invasive airway support and stimulation was necessary due to a diminished breathing effort and a heart rate below 100 bpm. After successful intervention, the patient stabilized under positive airway pressure support. The final APGAR score was 8/4/7. On examination, the most significant findings were a systolic murmur, a cleft palate, retroglossia, as well as low set ears, a small nose, and narrow mouth. Initial postnatal echocardiography demonstrated a persistent large circular pericardial effusion along with a significantly reduced contractility, severe tricuspid, and mitral valve insufficiency.

Nine hours after birth, the patient’s condition suddenly deteriorated to the point of cardiorespiratory collapse most likely due to complete myocardial insufficiency. Cardiopulmonary resuscitation leads to return of spontaneous circulation and later full stabilization of the patient’s condition.

In the first days of life, further diagnostic measures lead to the diagnosis of bilateral congenital cataract, requiring further operative treatment at 3 months of age. After breathing support could be ceased, sensorineural hearing loss was diagnosed at 4 weeks of life by brain evoked response audiometry, which was treated with hearing aids and early intervention. In addition, paracentesis and insertion of grommets was performed to prevent fluid collections and achieve better aeration of the middle ear, which can be impaired due to the cleft palate. Re-evaluation for cochlear implants took place at 8 months of age, the latter were implanted at 12 months of age.

The pericardial effusion was in a steady state until it seemed to increase at around 6 weeks of life leading to an unstable clinical condition. Echocardiography showed a “swinging heart,” meaning a counterclockwise rotational movement added to the usual triangular movement of the heart leading to a dance-like movement, and signs of pulmonary hypertension with urgent indication for drainage and further diagnostics in search for an etiology. Thoracic magnetic resonance imaging reinforced the indication for drainage and could exclude a tumor as cause of the effusion. Drainage of in total 70 ml of fluid was performed and material was sent for histological examination. Results showed no signs of malignancy, chyle, or infection as the reason for the effusion. However, analysis of interleukin-6 (IL-6), IL-8, and IL-10 levels showed significant elevation of pro- and anti-inflammatory cytokines (Figure 1), with only slight elevation of leucocytes (21/μl) mainly constituting of lymphocytes (20/μl).

![FIGURE 1 Pro- and anti-inflammatory cytokines in the pericardial effusion at Day 46 and Day 82 of life: Day 46: IL-6: 206.88 pg/ml (reference range: 4.11–3000); IL-8: 108.06 pg/ml (2.74–2000); IL-10: 311.33 pg/ml (4.11–3000); day 82: IL-6: 162.74 pg/ml; IL-8: 80.52 pg/ml; IL-10: 299.61 pg/ml.](image)

Reviewing all clinical features (congenital cataract, hearing loss, dysmorphic features, isolated pericardial effusion), and after exclusion of congenital disorders of glycosylation (CDG), we settled on the clinical diagnosis of Aymé-Gripp syndrome.

The pericardial effusion was recurrent to pre-drainage levels but with a clinically stable patient. Eventually pericardial fenestration was performed at 3 months of age, with permanent resolution of the effusion.

Magnetic resonance imaging of the brain revealed a normal anatomy of the brain and neurocranium. Ultrasound of the abdominal organs was unremarkable. With clinical diagnosis of Aymé-Gripp syndrome, trio exome sequencing was performed revealing a heterozygous missense variant c.173C>T, p.Thr58Ile in the MAF (ENST00000326043):c.[173C>T];[=], p.[(Thr58Ile)];[=]. GRCh37 previously reported to be associated with Aymé-Gripp syndrome (OMIM #601088) (Niceta et al., 2015). Exome sequencing of the parents showed wild-type sequence rendering the variant to be de novo. It was classified as pathogenic (Class 5) in accordance with the recommendations of the American College of Medical Genetics and Genomics due to it being previously described as clinically relevant (Niceta et al., 2015).

At present, the child is under further treatment for his sensorineural hearing loss and his cataract. Multidisciplinary follow-up includes neurodevelopmental follow-up, ears nose and throat (ENT), ophthalmology, and pediatric cardiology.

At last evaluation in our center for developmental pediatrics at 12 months of age, he showed global developmental delay. Especially central and peripheral hypotonia including head lag were observed. At the time he measured weight 7170 g (< 3rd centile), length 75 cm (25th centile), head circumference 45 cm (3rd–10th centile).

### DISCUSSION

Aymé-Gripp syndrome describes a triology of early onset cataracts, sensorineural hearing loss, and distinct facial features initially
described as Down syndrome-like caused by a pathogenic mutation in the MAF gene. The name was suggested by Niceta et al. (2015) in 2015 who described the genetic changes leading to this clinical presentation which was first described separately by Aymé and Philip (1997) and Gripp et al. (1996) in the mid-1990s. As of now, 21 patients have been described with disease-causing variants in the MAF (Alkhunaizi et al., 2019; Shivarajan M. Amudhavalli et al., 2018; Niceta et al., 2020). Niceta et al. (2015) described eight different variants of which “Individual 4” presented with the same variant as the patient described here but without pericardial effusion at the time of diagnosis at the age of 22 months.

In a substantial number of cases, a pericardial effusion of varying degree has been described, the leading phenotypic feature in the here described case (S.M. Amudhavalli et al., 2020; Shivarajan M. Amudhavalli et al., 2018; Niceta et al., 2015).

Congenital pericardial effusions are rare and most commonly occur with structural heart disease, hydrops fetalis of varying cause, cardiac or extra-cardiac malignancies, or malformations (Slesnick et al., 2005). Due to the combination of pericardial effusion with the first two key features of the syndrome and after exclusion of common causes of fetal pericardial effusion, the clinical diagnosis of Aymé-Gripp syndrome was established and later verified by exome sequencing.

The literature so far described eight patients with Aymé-Gripp syndrome who presented with pericarditis or pericardial effusion of varying degree. Four of them presented in the neonatal period, one so severe requiring effusion aspiration and eventually a pericardial fenestration like the patient presented here (S.M. Amudhavalli et al., 2020; Shivarajan M. Amudhavalli et al., 2018). As to our knowledge, in none of these patients a pericardial effusion has been reported prenatally although it could be possible that due to limited prenatal screening an effusion might have gone unnoticed in these cases. If the pericardial effusion has been as large as in our case, it is unlikely to go unnoticed since it had impacted heart function in such a degree that cardiopulmonary resuscitation was necessary within the first 24 h of life.

In five of the patients presenting with pericardial effusion or pericarditis, the MAF variant found was c.176C>T, p.Pro59His (Shivarajan M. Amudhavalli et al., 2018; Niceta et al., 2015, 2020), which could be interpreted as strong association between the mutation and this particular presentation of Aymé-Gripp syndrome. All reported variants causing the syndrome, including those with pericarditis or pericardial effusion in the phenotype, are located in the N-terminal transactivation domain of MAF (Niceta et al., 2015).

Interestingly, c-MAF has been previously described to act as a transcriptional activator or repressor, depending on the binding site and binding partner (Xu et al., 2018). This leucine zipper-containing transcription factor drives the regulation of several cellular processes, including embryonic lens fiber cell development, increased T-cell susceptibility to apoptosis, and chondrocyte terminal differentiation (Pathania et al., 2016). In patients with molecular diagnosis of Aymé-Gripp syndrome, the cause and origin of persistent pericardial effusion remains unknown. Here, we found significantly increased levels of IL-6, IL-8, and IL-10. Previously, c-MAF has been found to be essential for IL-10 gene expression in B cells (Liu et al., 2018). IL-6, however, plays a unique role in initiating c-MAF expression after T-cell receptor engagement (Yang et al., 2005). Previous studies were able to show (Lyon et al., 2003; Niceta et al., 2015) that (de novo) missense variants in MAF exert a distinct, dominantly acting effect affecting multiple organs and tissues. Hence, our findings suggest that the c-MAF-activating effect causes upregulation of c-MAF expression driving a secondary proinflammatory pericardial environment with persistent pericardial effusion.

The facial features of our patient as seen in Figure 2 did show a short nose and narrow mouth as well as low set ears and retrognathia, narrow mouth, and short nose (d)

**FIGURE 2** Prenatal ultrasound with the pericardial effusion at 36 weeks of gestation (a), postnatal MRI with large circular pericardial effusion at Day 45 (b), prenatal ultrasound of facial features at 22 weeks of gestation (c), and with 8 months of age (notice low set ears, retrognathia, narrow mouth, and short nose) (d)
CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
Anna-Lina König, Hemmen Sabir, Miriam Bertrand, Ute Grasshoff, and Eugenia Bernis performed genetic and expression studies. Brigitte Strizek, Ulrike Herberg, Gesa Wiegand, Cornelia Wiechers, Heiko Reutter, and Andreas Müller recruited and performed the clinical examinations of the index case. Anna-Lina König, Hemmen Sabir, Heiko Reutter, and Andreas Müller designed and oversaw the entire study and wrote the manuscript.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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