Pulmonary granulomatosis of genetic origin

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Pulmonary granulomatosis of genetic origin mostly occurs in immunodeficiency disorders and autoinflammatory conditions. In addition to specific approaches in this regard, the diagnostic workup needs to cover environmental and occupational aspects.

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Abstract
Granulomatous inflammation of the lung can be a manifestation of different conditions and can be caused by endogenous inflammation or external triggers. A multitude of different genetic mutations can either predispose patients to infections with granuloma-forming pathogens or cause autoinflammatory disorders, both leading to the phenotype of pulmonary granulomatosis. Based on a detailed patient history, physical examination and a diagnostic approach including laboratory workup, pulmonary function tests (PFTs), computed tomography (CT) scans, bronchoscopy with bronchoalveolar lavage (BAL), lung biopsies and specialised microbiological and immunological diagnostics, a correct diagnosis of an underlying cause of pulmonary granulomatosis of genetic origin can be made and appropriate therapy can be initiated. Depending on the underlying disorder, treatment approaches can include antimicrobial therapy, immunosuppression and even haematopoietic stem cell transplantation (HSCT). Patients with immunodeficiencies and autoinflammatory conditions are at the highest risk of developing pulmonary granulomatosis of genetic origin. Here we provide a review on these disorders and discuss pathogenesis, clinical presentation, diagnostic approach and treatment.

Introduction
Granulomas are defined as focal, organised inflammatory infiltrates of epithelioid histiocytes (macrophages). They may contain multinucleated giant cells, lymphocytes and plasma cells, as well as necrotic areas [1, 2]. Granulomas are formed to encapsulate material or pathogens that cannot be eliminated otherwise, but in some cases the exact causes for granuloma formation are still unclear [1, 2]. Granulomas can occur in different disorders and therefore warrant a careful evaluation of the clinical context [1]. Histologically, necrotising and non-necrotising granulomas are differentiated. Necrotising granulomas develop more commonly in association with an infectious cause [1]. Morphology, localisation and proof of infectious agents can give additional clues to the underlying diagnosis.

Pulmonary granulomatous inflammatory conditions comprise a heterogeneous group of diseases with different pathologies, phenotypes and prognoses [1]. Infectious and noninfectious causes have to be differentiated. Mycobacterial infections (both Mycobacterium tuberculosis and nontuberculosis (non-TB))
mycobacteria) and fungal infections (histoplasma, cryptococcus, pneumocystis and aspergillus) are the most common infectious triggers associated with pulmonary granuloma formation. Noninfectious pulmonary granulomatous diseases encompass autoinflammatory conditions (e.g. sarcoidosis), granuloma formation after environmental exposure (e.g. chronic beryllium disease), vasculitis (e.g. granulomatosis with polyangiitis), autoimmune diseases and primary immunodeficiencies (see table 1 for an overview of the conditions discussed in this review) [1, 2]. Non-necrotising granulomas more commonly develop in cases without apparent infectious triggers, with the exception of granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis (table 1) [1, 2].

Key for diagnosis of the underlying condition is not only the presence of pulmonary granulomas but a combination of typical clinical features, laboratory parameters, pulmonary function tests (PFTs), histologic assessment and imaging studies. Evaluation of affected lung tissue is the gold standard in accessing pulmonary granulomatous disease and might even be essential in identifying infectious causes in some conditions [1, 3]. Specimens can be obtained by bronchoscopy with bronchoalveolar lavage (BAL), transbronchial biopsy, cryobiopsy, or video-assisted thoracoscopic surgical (VATS) biopsy. VATS biopsy seems superior to transbronchial biopsy in establishing the correct diagnosis [4–6]; however, VATS should only be performed if a histological result is paramount for treatment decisions, especially in paediatric patients [3, 7, 8]. If granulomatous infiltration is present in organs that are more easily accessible for biopsy (e.g. the skin) then these sites should be preferred for sampling. As lung biopsies are not always readily available in the clinical setting, primary evaluation with high-resolution computed tomography (HRCT) chest scans is used to appreciate suspected granulomatous inflammation of the lung [8, 9]. Imaging techniques such as positron emission tomography (PET)–computed tomography (CT) might allow identification of additional sites with active lymphoproliferation that may be more easily accessible for biopsy (e.g. peripheral lymph nodes) [8]. Additional laboratory workup may reveal immunological abnormalities or hint at autoinflammatory conditions. PFTs are warranted to assess the clinical course of pulmonary involvement; however, there is no consensus on the best diagnostic algorithm for all cases of granulomatous lung disease and decisions need to be made on an individual basis.

This review focuses on genetic causes of pulmonary granulomatosis and respective disorders are presented here with regard to genetic, clinical, diagnostic, histologic and therapeutic aspects.

**Primary immunodeficiencies associated with pulmonary granulomatosis**

Common variable immunodeficiency (CVID) comprises a heterogeneous group of primary immunodeficiencies with hypogammaglobulinaemia and variable T-lymphocyte/B-lymphocyte dysfunction [10]. CVID typically manifests in young adulthood and is the most common primary immunodeficiency with a prevalence of 0.7 per 10 000 [11, 12]. Monogenetic causes of CVID have been identified in up to 50% of cases, with mutations in nuclear factor κ-light-chain-enhancer of activated B-cells 1 (NF-κB1) and transmembrane activator and calcium-modulating ligand (CAML) interactor (TACI) being the most common [13–18].

Diagnostic criteria for CVID include hypogammaglobulinaemia less than two standard deviations (SD) below the mean for age. Additionally, a reduction of immunoglobulin (Ig)A/IgM, onset of symptomatic immunodeficiency at greater than 2 years of age, absent isohaemagglutinins and/or poor response to vaccination, as well as exclusion of other defined causes of hypogammaglobulinaemia, constitute the criteria for CVID [19]. Patients typically suffer from recurrent bronchopulmonary infections and additional autoimmune phenomena are present in up to 40% of cases [10, 20]. A complication of CVID is granulomatous-lymphocytic interstitial lung disease (GLILD), characterised by granulomatous and lymphoproliferative inflammation of the small airways and pulmonary interstitium (figure 1) [1]. GLILD is considered to be a pulmonary manifestation of a systemic granulomatous disease that also includes other organs. Dyspnoea and recurrent bronchopulmonary infections are apparent in affected patients [8] and a restrictive pattern and reduced diffusing capacity of the lung for carbon monoxide (DLCO) can be observed in PFTs [21]. Up to one third of patients with CVID can develop GLILD [8] and GLILD in patients with CVID is associated with a poorer prognosis and higher mortality [22].

On histopathological evaluation, GLILD presents with lymphocytic interstitial pneumonitis, follicular bronchiolitis and non-necrotising granulomas [8]. These changes are typically found in the lower lobes of the lungs. A mix of both peribronchiolar and interstitial lymphoid infiltration is seen, predominantly by CD4+ T-cells but also by B-cells [23]. GLILD is also associated with cryptogenic organising pneumonia and interstitial fibrosis [23] and the latter may show a progressive course [22, 24].
| Condition | Exemplary clinical features | Exemplary laboratory features | Radiologic presentation | Histology |
|-----------|-----------------------------|-------------------------------|------------------------|-----------|
| **CVID**  | Recurrent bronchopulmonary infections Lymphoproliferation | Hypogammaglobulinaemia | GLILD Small and large nodules Round infiltrates ("reversed halo" or "atoll" signs) GGOs (mainly in the lower lobes) | Interstitial pneumonitis Follicular bronchiolitis Non-caseating granulomas Lymphoid infiltration |
| **LRBA/CTLA-4 deficiency** | Autoimmunopathies (lymphoproliferation, enteropathy, cytopenias) Respiratory infections CNS involvement | Hypogammaglobulinaemia Cytopenias Functional T-cell defects | See CVID | See CVID |
| **CGD**   | Recurrent infections Skin and organ abscesses | Reduced "respiratory burst" | Infiltrates Abscesses Pneumatocoles Bronchiectasis obliterative bronchiolitis | Changes associated with inflammatory infiltrates, abscesses and fibrosis Non-caseating granulomas |
| **STAT3 loss of function (AD HIES)** | Dermatitis, skin abscesses Tooth retention Coarse facial features Bronchopulmonary infections | ↑ IgE (>2.000 units·mL⁻¹) ↓ Th17 cells ↓ Memory B cells ↓ Production of inflammatory cytokines (IL-17/IL-22) | Abcesses Pneumatocoles Chronic pneumothorax Granulomas | Changes associated with inflammatory infiltrates, abscesses and fibrosis Non-caseating granulomas |
| **STAT3 gain of function** | Autoimmunopathies (cytopenias, lymphoproliferation, enteropathy, diabetes) | Cytopenias Hyperglycaemia Impaired T-cell signalling | Lymphocytic interstitial pneumonitis Granulomas Pulmonary fibrosis Cryptogenic organising pneumonia | Lymphocytic interstitial pneumonia Non-necrotising granulomas Fibrosis |
| **MSMD**  | Mycobacterial infections Infection by intracellular pathogens Chronic mucocutaneous candidiasis | Reduced IFN-γ production | Focal infiltration of upper lobes, middle lobes, or lingula Pulmonary granulomas as in mycobacterial infection Cavernas Lymphadenopathy | Necrotising granulomas in *Mycobacterium tuberculosis* Varying histology in non-*M. tuberculosis* mycobacteria (necrotising and non-necrotising) Random or bronchocentric location of granulomas |
| **Blau syndrome/early onset sarcoidosis** | Classical triad (granulomatous polyarthritis, dermatitis, uveitis) 50% fever, lymphadenopathy, vasculitis | ↑ Inflammatory cytokines ↑ ACE, sCD25, neopterin BAL (lymphocytosis, CD4:CD8 ratio >3.5:1) | GGOs Micronodules Granulomas | Non-necrotising granulomas |
| **NOD2-associated autoinflammatory disease** | Recurrent fever Weight loss Non-erosive arthritis Granulomatous dermatitis Granulomatous colitis | Anaemia Leukocytosis Elevated inflammatory cytokines | GGOs Micronodules Granulomas | Non-necrotising granulomas |
| **Chronic beryllium disease** | Dry cough Shortness of breath Malaise Fatigue | Positive beryllium lymphocyte proliferation test | Nodules GGOs, thickened septal lines Bronchial wall thickening Lymphadenopathy | Non-necrotising granulomas Mononuclear cell infiltrates |
Small and large nodules, consolidations and ground-glass abnormalities can be found on HRCT; additionally, a lymphadenopathy is often present [21]. Lung biopsies are recommended to establish a definitive diagnosis of GLILD and to rule out differential diagnoses including infectious causes, interstitial pneumonia, sarcoidosis, cryptogenic organising pneumonia, lymphoma and others [8].

In CVID, Ig replacement therapy is indicated to reduce susceptibility to bronchopulmonary infections. In GLILD, corticosteroids alone do not lead to durable improvement [8]; however, combined targeting of T-cells and B-cells with azathioprine and rituximab improves both radiographic pathology and PFTs in patients with CVID and GLILD [25]. Long-term therapy is needed to establish stable remission and several trials are currently exploring alternative immunosuppressive treatment strategies, including the use of T-cell activation blocking agents like Abatacept.

**Combined immunodeficiencies**

Combined immunodeficiencies (CIDs) are a heterogeneous group of disorders with reduced but not absent T-cell immunity. CID-associated mutations have been found in Caspase10, PI3KCD, ITK, Dock8 and others [26]. There is considerable overlap with both severe combined immunodeficiencies (SCIDs) on one end of the spectrum and CVID on the other [19, 26]. Patients with CID may therefore present with SCID-like phenotypes, which require urgent haematopoietic stem cell transplantation (HSCT), but milder phenotypes can also occur, making treatment decisions difficult. If susceptibility to infection or autoimmunity are present, patients can be classified as having profound combined immunodeficiencies (PCIDs). Some 7% of patients with PCID have been found to suffer from chronic lung disease, including from GLILD [26]. Three disorders are discussed here in more detail, as follows: 1) null mutations in recombinase activating gene 1 or gene 2 (RAG 1 or RAG 2). These mutations cause SCID; however, hypomorphic mutations with residual RAG activity can lead to a PCID classified as atypical SCID [26–28]. Systemic granulomatous inflammation is a hallmark of the disorder. Interstitial pneumonia with noncaseating epithelioid-cell granulomas has also been reported in RAG deficiency [28]; 2) cytotoxic

| Condition | Exemplary clinical features | Exemplary laboratory features | Radiologic presentation | Histology |
|-----------|-----------------------------|-------------------------------|-------------------------|-----------|
| SAVI      | Constant fever in infancy   | Constantly ↑ acute phase/ inflammation parameters | Nodules/Cavities/Fixed infiltrates | Mixed lymphocytic infiltrate/Interstitial fibrosis/Empysema |
| Granulomatosis with polyangiitis | Rhinitis, otitis, Cough, Stridor, Obstruction, Dyspnea | ↑ Cytoplasmic ANCAs | Nodules/granulomas/Cavities/Pleural effusions/Lymphadenopathy | Necrotising granulomas/Necrotising vasculitis |
| Eosinophilic granulomatosis with polyangiitis | Asthma, Vasculitis, Cutaneous, intestinal, cardial granulomas | ↑ Perinuclear ANCAs | Nodules/granulomas/GGOs/Bronchial wall thickening/Consolidations | Necrotising granulomatous inflammation/Eosinophilic infiltration |
| Hypersensitivity pneumonitis | Acute onset (fever, cough, tachypnoea), Subacute/chronic (productive cough, fatigue, malaise, chronic cyanosis) | ↑ Specific IgGs against organic compounds | Centrilobular GGOs/Nodular opacities/air-trapping/Mosaic attenuation/Septal thickening/Bronchiectasis/Honeycombing | Poorly-formed non-caseating granulomas/Bronchiolitis with lymphocytic infiltration/Fibrotic nonspecific interstitial inflammation/Lymphocytic infiltrates/Poorly-formed granulomas |

CVID: common variable immunodeficiency; GLILD: granulomatous-lymphocytic interstitial lung disease; GGO: ground-glass opacity; LRBA: lipopolysaccharide-responsive beige-like anchor protein; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; CNS: central nervous system; CGD: chronic granulomatous disease; STAT-3: signal transducer and activator of transcription 3; Ig: immunoglobulin; AD: autosomal-dominant; HIES: hyper IgE syndrome; IL: interleukin; MSMD: Mendelian-susceptibility to mycobacterial disease; IFN: interferon; ACE: angiotensin-converting enzyme; BAL: bronchoalveolar lavage; NOD2: nucleotide-binding oligomerisation domain-containing protein 2; STING: stimulator of interferon genes; SAVI: STING-associated vasculopathy with onset in infancy; ANCA: anti-neutrophil cytoplasmic antibody.

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T-lymphocyte-associated protein 4 (CTLA-4) deficiency; and 3) lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency [20]. These latter two disorders are clinically very similar conditions that have been classified as CVID but may show some aspects of CID. LRBA regulates intracellular trafficking of CTLA-4 [29]. Both LRBA and CTLA-4 deficiency lead to impaired downregulation of immune processes [20, 29]. The clinical phenotype of both disorders is similar: autoimmune cytopenias as well as autoimmune inflammation in the intestines, the central nervous system (CNS) and other organs has been reported [30–32]. GLILD has been found in up to two thirds of patients with CTLA-4 deficiency and also in patients with LRBA deficiency (figures 2a–2c) [30, 31]. Diagnostic workup should follow the standards outlined above.

**FIGURE 1** Alveolar haemorrhage: partly epithelioid cellular interstitial inflammation in the affected lung, suggestive of a mild granulomatous-lymphocytic interstitial lung disease (GLILD). Airspaces are filled with erythrocytes (a), as indicated by an exemplar asterisk, some cluster forming alveolar macrophages (a) and (c), as indicated by arrowheads, the latter using CD68 stain) and small non-necrotising interstitial granulomas (b), as indicated by arrowheads) consisting of a few epithelioid cells and lymphocytes. Interstitial lymphocytic infiltrate mainly consists of CD4 T-cells, partly clustered (d) and partly scattered (e). CD8 T-cells are scattered (f) and form the minority of the lymphocytic infiltrations. Scale bars: a–c, e, f) 50 μm; d) 200 μm.
CTLA-4 fusion proteins (e.g. abatacept) and mammalian target of rapamycin (mTOR) inhibitors have been used successfully in both LRBA and CTLA-4 deficiency and these treatments have had positive effects on GLILD as well [29, 30, 33]. Severe infectious or autoimmune complications in CIDs that cannot be controlled by Ig replacement or immunosuppressive therapy can be an indication for HSCT [26]. Improvement of GLILD after stem cell transplantation (SCT) has been demonstrated in CTLA-4 deficiency (figure 2d) [30]. Symptoms of mild RAG deficiency can be controlled by immunosuppression but long-term remission cannot be achieved in all patients. Some cases of partial RAG deficiency, especially atypical SCID, can only be cured with SCT [27, 28]. The diverse phenotype of (P)CIDs and the individual clinical course has therefore to be taken into account to decide whether SCT might be a viable option for affected patients [26, 27].

Chronic granulomatous disease
Chronic granulomatous disease (CGD) is caused by defects in superoxide-generating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase of phagocytes and lymphocytes [34, 35]. Currently, five different affected genes are known, while the most common findings are mutations in gp91phox (CYBB,
cross-linked). Autosomal recessive forms involve mutations in p22phox (CYBA), p47phox (NCF1), p67phox (NCF2) and p40phox (NCF4) [34–36]. Both impaired killing of bacteria and fungi, as well as prolonged autoinflammatory reactions with granuloma formation, can occur [34, 35]. About one to three in 200,000 newborns are affected by CGD [36].

Pulmonary manifestations represent the most common organ involvement in CGD. Infectious complications are found in 80% of CGD patients, mostly in the form of pneumonia [37, 38]. Formation of abscesses, bronchiectasis and pulmonary granulomas has also been reported (figure 3) [3, 39]. Increased secretion of pro-inflammatory mediators or decreased production of anti-inflammatory cytokines causes inflammatory or auto-inflammatory manifestations in CGD [40]. This can lead to development of granulomas in multiple organs, such as the brain, liver, gastrointestinal tract, spleen, or lung. Granulomas are noncaseating and contain multinucleated giant cells [37]. Whether or not an infection is essential to trigger this inflammatory cascade is still debated [34]. Pulmonary symptoms in patients with CGD include dyspnoea, cough and reduced exercise tolerance [34, 35].

CT scans are important for visualisation of pulmonary pathologies in CGD (table 1); however, lung biopsies might be essential to correctly identify infectious triggers of disease exacerbation (as has been shown for Burkholderia species [3]). PFTs may show obstructive or restrictive patterns depending on the extent of lung involvement [34, 35].

CGD is curable by HSCT and appropriate evaluations should be initiated as soon as the diagnosis is made [41, 42]. Until HSCT can be performed, control and prevention of infection is paramount in CGD. Removal of severely damaged pulmonary tissue is sometimes indicated and some experience exists in the use of steroids in combination with anti-infective drugs [43]. Some authors have suggested the use of tumour necrosis factor (TNF) inhibitors to control inflammation and granuloma formation [9].

**Mendelian susceptibility to mycobacterial disease**

Defects in the interferon-γ (IFNγ)/interleukin-12 (IL-12) pathway lead to Mendelian susceptibility to mycobacterial disease (MSMD). In MSMD, effective killing of intracellular pathogens is impaired [44, 45]. Currently, mutations in 15 different genes (IFNGR1, IFNGR2, STAT1, JAK1, IRF8, SPPL2A, IL12B, IL12RB1, IL12RB2, IL23R, ISG15, TYK2, RORC, CYBB and NEMO) have been reported in MSMD.
although these account for only around 50% of cases [44]. Prevalence is estimated to be around one in 50,000 [46]. Patients present with mycobacterial infections, classically from Bacillus Calmette–Guérin (BCG) vaccine or non-TB mycobacteria. Infections by M. tuberculosis and other intracellular pathogens are common, as is chronic mucocutaneous candidiasis (for specific genetic defects) [44, 46]. Clinical presentation varies from localised to systemic manifestations and via an acute or chronic course. Pulmonary granuloma formation develops as frequently as in pulmonary mycobacterial infection and both necrotising and non-necrotising granulomas are found [44, 46]. Impaired cytokine secretion after leukocyte stimulation and reduced cell-surface/intracellular expression of receptors/proteins involved in the IFN-\(\gamma\) pathway, can help in identifying specific targets for genetic analysis [45]. Prolonged treatment with antimycobacterial antibiotics is essential to control infections and additional IFN-\(\gamma\) therapy can be helpful. In some cases, surgical removal of pulmonary lesions is indicated and in severe cases HSCT has been successful [46, 47].

**STAT3 loss of function**

Loss of function mutations in the signal transducer and activator of transcription 3 (STAT3) cause STAT3 autosomal-dominant (AD) hyper IgE syndrome (HIES) [48–51]. In STAT3 HIES, impaired neutrophil chemotaxis, reduced production of inflammatory cytokines and defective repair mechanisms of bronchiolar and alveolar epithelial cells are pathogenic factors [52–55]. STAT3 HIES is a rare immunodeficiency with an incidence of less than one in 1,000,000 [56].

STAT3 HIES patients present with typical coarse facial features, eczematous dermatitis, retention of primary teeth, scoliosis and joint hyperextensibility, as well as with immunodeficiency and recurrent bronchopulmonary infections [55]. Pulmonary granuloma formation as well as bronchiectasis, pneumatoceles and cavernas in these patients have been attributed to recurrent infections and to impaired lung remodelling mechanisms [55].

Imaging studies, especially chest CT scans, are essential in establishing the extent of pulmonary involvement [55]. Therapeutic options include antimicrobial prophylaxis with trimethoprim-sulfamethoxazole, as well as early aggressive treatment of infections with antibiotics [52]. Ig replacement therapy has been shown to reduce pulmonary complications if IgG levels are low or serological responses to vaccination are missing [57]. Surgical excision of large pneumatoceles might be indicated [52].

**STAT3 gain of function**

Gain of function mutations in STAT3 cause early onset immunodeficiency with additional features such as autoimmune enteropathy, diabetes mellitus, autoimmune cytopenias, lymphadenopathy, splenomegaly, short stature and interstitial lung disease (ILD) [58–61]. Currently, less than 50 cases have been described [58]. Granulomatous lung disease has been reported in at least two affected individuals, but other forms of ILD seem to be a more common feature in patients with gain of function STAT3 mutations [58, 62, 63]. Therapeutic options include immunosuppression with anti-IL-6 agents and Janus kinase (JAK) inhibitors, while SCT has not yielded convincing results [58, 64]. STAT3 inhibitors are currently being tested clinically and might become a therapeutic option for patients with STAT3 gain of function in the future [58].

**Other immunodeficiencies**

Patients with XIAP and GATA2 deficiencies have been shown to develop GLILD, as have patients with Kabuki syndrome and those with IgA/IgG2 deficiencies [65–67]. GLILD was successfully treated with rituximab and azathioprine in at least one patient with XIAP deficiency [67].

Patients with caspase 8 deficiency, Rhoh deficiency, TAP1/TAP2 deficiency and Good’s syndrome have been shown to develop pulmonary granulomas [66, 68–71]. Granulomatous lung disease has also been reported in some cases of haemophagocytic lymphohistiocytosis (HLH) [72–74]. Treatment decisions have to be individualised based on the specific defect and the clinical situation of the patient.

**Autoimmune and autoinflammatory diseases associated with pulmonary granulomatosis**

**Sarcoidosis**

Sarcoidosis is an inflammatory disorder of unknown cause that is characterised by granuloma formation in the affected organs, most often in the lungs [75] although any organ can be affected. The incidence and prevalence of sarcoidosis, as well as its clinical presentation, vary greatly across geographical regions and between the sexes, aw well as between different ethnicities and age groups. Its prevalence varies between two and 1160 per 100,000 and is highest in Scandinavia and in African-American populations [76–78].
The disease develops in genetically predisposed individuals with exposure to an as-yet unknown antigen. Genome-wide association studies have identified human leukocyte antigen (HLA) class II alleles and several non-HLA genes as susceptibility factors [79–82]. Most interestingly, a polymorphism in the TNF gene confers resistance to anti-TNF therapy [83]. Recently, defects in autophagy, JAK STAT signalling and mTOR pathways have been identified as playing a crucial role in ineffective clearance of infectious agents or nonorganic particles, triggering granuloma formation due to macrophage and T-cell dysfunction [84, 85]. Familial aggregation is known and having a family member with the disease is associated with a two-to-four-fold increased risk of developing sarcoidosis [86]. Although these findings are significant, there is no application of this genetic knowledge in everyday clinics.

The pathological hallmark of sarcoidosis is the presence of compact, epithelioid, non-necrotising granulomas with varying degrees of lymphocytic inflammation. This is used, in combination with a compatible clinical disease manifestation and typical radiological presentation, as a diagnostic parameter. Nevertheless, other causes of granuloma need to be excluded [87]. These inflammatory processes attract mononuclear and polymorphic nuclear cells to the lower respiratory tract, which can be probed by BAL. An increase in lymphocytes with an elevated CD4/CD8 ratio heralds a spontaneous resolution or a desirable course under therapy, but an increase in neutrophils is associated with progressive disease requiring therapy [88]. PFTs may reveal reduced diffusion capacity and a restrictive pattern with loss of vital capacity, but also obstructive changes [89].

Corticosteroids still constitute the first line treatment in cases with progressive organ damage [75, 87]. Corticosteroid-sparing agents, such as azathioprine or methotrexate, are frequently used when prolonged therapy is necessary [90, 91]. Studies and case series demonstrate the successful use of newer agents which manipulate the cytokine network, such as infliximab, rituximab, or JAK-inhibitors such as tofacitinib [92–97]. None of these are approved but off-label therapy is often initiated [75].

**Blau syndrome/early-onset sarcoidosis**

Both Blau syndrome and early-onset sarcoidosis are rare disorders caused by gain of function mutations in the nucleotide-binding oligomerisation domain-containing protein 2 (NOD2) pattern recognition receptor (also known as the caspase-recruitment domain-containing protein 15 (CARD-15)) [98–100]. NOD2 is involved in innate immune responses and the inflammative cascade after viral or bacterial infections (via NF-κB and TNF receptor-associated factor 3 (TRAF3)) [101, 102]. Gain of function mutations in NOD2 are associated with granulomatous inflammation of affected tissues, though a triggering infection is possibly essential [100, 103, 104]. Histologic evaluation reveals epithelioid cell-rich, noncaseating granulomas [105].

Blau syndrome is the inherited form of the disease and early-onset sarcoidosis is caused by *de novo* mutations in NOD2. The clinical course of the two entities is phenotypically indistinguishable and patients show a triad of granulomatous polyarthritis, dermatitis and uveitis [99, 103, 106–108] (figure 4). Most patients present under the age of 2 years [109] and about one third to one half of patients have additional manifestations. These include fever, lymphadenopathy, vasculitis, arterial hypertension, transient neuropathies, granulomatous kidney disease and granulomatous liver disease, as well as pulmonary embolisms [107, 110]. At least four patients with Blau syndrome and interstitial/granulomatous lung disease have been described [100, 107, 111]. Clinical signs were mild or not present and the pulmonary changes were found by chance on CT scan [111]. Pulmonary involvement in early-onset sarcoidosis is less frequent than in later-onset sarcoidosis. One patient has been reported with bronchial granulomas [112], one with bronchial granuloma and subsequent pulmonary haemorrhage [113] and one with pulmonary micronodules [114].

Parameters that have been helpful in diagnosing sarcoidosis are serum levels of angiotensin-converting enzyme (ACE), soluble IL-2 receptor and serum amyloid A [103, 115]. For patients with high suspicion of Blau syndrome/early-onset sarcoidosis, genetic analysis should be performed (figure 4) [107]. A HRCT chest scan is paramount in identifying pulmonary involvement. If patients undergo bronchoscopy, the cellular composition of bronchoalveolar fluid should be analysed, as a lymphocytosis of >15% (as well as a CD4/CD8 ratio of >3.5:1) suggests pulmonary sarcoidosis or pulmonary involvement in Blau syndrome [116].

Therapeutic approaches with corticosteroids, anti-TNF agents and anti-IL-1 therapy have yielded positive results in halting inflammation; however, there is no consensus regarding optimal therapy so far [109, 110, 117].

**NOD2-associated autoinflammatory disease**

A similar clinical picture to that in Blau syndrome can be found in NOD2-associated autoinflammatory disease (NAID), which is caused by the IVS8+ NOD2 variant or the heterozygous p.T189M and p.R703C
NOD2 variants [118]. Less than 100 cases, mainly adult Caucasian patients, have been reported, who suffer from recurrent fever, weight loss, nonerosive arthritis, granulomatous dermatitis and granulomatous colitis [119, 120]. Pleuritis in several and non-necrotising pulmonary granulomas in at least one patient were also described [118, 120, 121]. Immunosuppression with corticosteroids or sulfasalazine has been effective, as has therapy with biologicals such as infliximab, tocilizumab and canakinumab [120].

Chronic beryllium disease

Inhaled beryllium can induce a cell-mediated or delayed hypersensitivity reaction in individuals with specific HLA-DPB1 polymorphisms and probably TNF-α polymorphisms. For the HLA-DPGlu69 variant, a direct interaction of beryllium has been shown via binding to the HLA molecule and eliciting of an IFNγ response [122–125]. Additional genetic risk factors might be present in individuals who develop beryllium sensitisation or chronic beryllium disease (CBD), as the above mentioned genotypes are also common in the general population [124, 126–129]. CBD is an occupational pulmonary granulomatous disease. Relevant exposure to beryllium can occur in manufacturing industries such as defence, aerospace, nuclear, automotive and electronics [130, 131]. Higher exposure puts patients at higher risk for CBD [129], but only 1–5% of exposed persons develop the disease, with a higher frequency in persons with the above mentioned polymorphisms [128, 132, 133]. CBD only rarely occurs in the general population, most frequently in persons living close to a beryllium processing plant or with family members that have been exposed to the contaminated clothes of beryllium workers [128, 134]. Patients are typically adults with a reported mean age at diagnosis of 44 years [131].

CBD is phenotypically indistinguishable from sarcoidosis and more than 6% of patients diagnosed with sarcoidosis might in fact suffer from CBD [131, 135]. Patients initially present with nonspecific symptoms, including dry cough and shortness of breath, that are similar to asthmatic symptoms, as well as less frequently with fever, fatigue, night sweats and weight loss [130, 136]. Imaging studies and PFTs reveal similar pathologies as in sarcoidosis. CBD should be considered if there is a history of beryllium exposure, beryllium sensitisation can be demonstrated (by a positive beryllium lymphocyte proliferation test) and there is evidence of noncaseating, poorly-formed granulomas and mononuclear cell infiltrates in lung biopsies [130].

Preventive measures have to be taken to reduce occupational beryllium exposure in persons with beryllium sensitisation [129]. The standard therapy for CBD is systemic glucocorticoids [130]. Patients with refractory disease or side-effects of glucocorticoid therapy might benefit from (additional) therapy with...
other immunosuppressive agents, such as methotrexate, azathioprine, or TNF antagonists, although evidence for this is limited [130, 137].

**STING-associated vasculopathy of infancy**

Gain of function mutations in the stimulator of IFN genes (STING) cause STING-associated vasculopathy with onset in infancy (SAVI) [138]. SAVI is considered rare with less than 20 cases reported so far [138–141].

Activation of STING by viral or bacterial triggers causes upregulation of IFNβ transcription, as well as upregulation of expression of other IFN-regulated genes leading to STAT1 phosphorylation. Patients with SAVI show uncontrolled STING activation, which causes early-onset constant fever, capillary vasculitis, lymphadenopathy, chronic anemia, failure to thrive, interstitial and granulomatous lung disease, or pulmonary fibrosis [139, 140, 142]. Pulmonary involvement especially differentiates patients with SAVI from other interferonopathies [141].

Chronic cough and tachypnoea manifest in the first weeks of life. Cutaneous manifestations typically show within the first 6 months. They include teleangiectatic, pustular or blistering exanthemas, mostly on acral sites like the fingers, nose and ears, but also on the cheeks [138]. ILD is found on CT scan (sometimes with nodular infiltrates) and restrictive patterns in PFTs have also been demonstrated [143]. Histologically, a mixed lymphocytic infiltrate, interstitial fibrosis and emphysema, as well as vasculitis, have been found in lung biopsies [138]. Pulmonary involvement is life-limiting in a significant number of patients [138, 139].

Different immunosuppressive therapies, including corticosteroids, cyclophosphamide, azathioprine, methotrexate, rituximab and infliximab, have shown only moderate beneficial effects [139]. As JAK inhibitors target the phosphorylation of STAT1/STAT2 [144], this pharmacological approach might be helpful in the future for patients with SAVI [138, 145].

**Granulomatosis with polyangiitis**

Granulomatosis with polyangiitis is an autoinflammatory systemic vasculitic disorder linked to polymorphisms in HLA-DPB1, HLA-DPA1, PRPTN3 and SERPINA1 [146]. Patients show elevated anti-neutrophil cytoplasmic antibodies (ANCAs) and, in 70–90% of cases, ANCA antibodies that target proteinase-3 are detected [147]. The pathogenesis of granulomatosis with polyangiitis is not fully understood; however, a combination of genetic susceptibility factors and environmental triggers may lead to a dysregulation of innate and adaptive immune responses [148].

Cytoplasmic ANCA associated vasculitis has an incidence of about 13–20·(1000000)−1·year−1 in adults and 0.45–6.39·(1000000)−1·year−1 in children [149, 150]. The diagnosis of granulomatosis with polyangiitis can be established following the established classification criteria with a combination of histological, serological and clinical findings [151, 152]. Pulmonary involvement is common in granulomatosis with polyangiitis [152, 153]. Typical symptoms include rhinitis, persistent otitis media, cough, stridor, obstruction, dyspnoea and haemoptysis. Subglottic or bronchial stenosis might develop secondary to inflammation.

Pulmonary nodules, cavities or fixed infiltrates are found in imaging studies [149, 154] and fluorodeoxyglucose (FDG)-PET/CT scan can help to appreciate the extent of the disease and to identify occult sites of inflammation [155]. Bronchoscopy is indicated if tracheal or bronchial stenosis is suspected and to obtain biopsies [105]. On histologic examination of affected tissues, necrotising granulomas with necrotising vasculitis are found [1]. Infectious causes contribute to a high morbidity and mortality in granulomatosis with polyangiitis and need to be ruled out and treated aggressively [105].

Control of autoinflammation can be achieved with a combination of high-dose corticosteroids and other immunosuppressive agents, such as cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil or rituximab [152].

**Eosinophilic granulomatosis with polyangiitis**

Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) is associated with polymorphisms of the Fcγ receptor 3B that is expressed on neutrophils and contributes to the clearance of immune complexes [156]. ANCA antibodies, which usually target myeloperoxidase (perinuclear (p-)ANCAs), can be detected in 30–75% of adult patients and around 30% of affected children [157, 158].

The incidence in adults is around 1–3·(1000000)−1·year−1 and less than 100 paediatric cases have been reported [157]. Asthma and eosinophilia are present in almost all patients with eosinophilic granulomatosis with polyangiitis and the most common misdiagnosis is therapy-refractive asthma. Vasculitis and granuloma
formation in the lungs, skin, digestive tract and heart are common in eosinophilic granulomatosis with polyangiitis [157, 159]. The condition has different phases of disease activity: a prodromal phase can be asymptomatic and is followed by an eosinophilic phase (where most paediatric patients are diagnosed); whereas adults are mainly diagnosed in the final vasculitic phase [157]. HRCT scan typically shows ground-glass opacities (GGOs), bronchial wall thickening, (micro)nodules and consolidations [157, 159]. Cytologic evaluation of BAL can demonstrate a mean eosinophilia of up to 33%, although patients may also present without eosinophilia [157, 159]. The histologic hallmark of eosinophilic granulomatosis with polyangiitis is necrotising granulomatous inflammation with eosinophilic infiltration, mainly of the small vessels of the upper and lower airways as well as the surrounding tissue, with formation of extravascular granulomas [159, 160].

Systemic corticosteroids, possibly in combination with azathioprine or cyclophosphamide, are recommended to control eosinophilic granulomatosis with polyangiitis [157, 161]. The IL-5 antibody mepolizumab has also yielded positive results in ANCA-positive patients with an eosinophilia of >150 cells·µL−1 [162].

**Other conditions**

Apart from the immunodeficiencies and autoinflammatory diseases presented here, there is growing evidence that other conditions that have some genetic background might predispose to pulmonary granulomatous inflammation. One example is histiocytosis X/Langerhan’s cell histiocytosis (LCH), a neoplastic process with inflammatory characteristics. Somatic mutations in BRAF and NRAS have been described in most patients with pulmonary LCH [163, 164]. Incidence of pulmonary LCH is around 0.27 per 100 000 and mostly affects young adults who smoke [165]. Clinical presentation is unspecific, involving dry cough, dyspnoea and fatigue [165]. Chest CT scans typically reveal stellate nodules, nodular opacities, cysts, or honeycombing [166] and these changes mainly occur in the middle and upper lobes of the lungs. BAL may yield CD1a and CD207 positive cells supporting the diagnosis [167]. Cessation of smoking is essential. Glucocorticoid therapy is successful only in some patients and others might need more aggressive chemotherapy (e.g. cytarabine or vinblastine) [167].

**Conclusions and further directions**

In this review we discuss the broad clinical and genetic spectrum of pulmonary granulomatosis of genetic origin. The diversity of conditions that can manifest in infants, children, adolescents and adults, based on specific genetic defects, is evident in the varying amount and type of granulomatous inflammation as well as the accompanying symptoms. These symptoms may give clues to the underlying disorder but can be nonspecific in many cases. Pathophysiology of granuloma formation is well understood in some of the diseases presented here and may be based on endogenous inflammation, impaired control of environmental pathogens, or pathological immune responses to harmless antigens. In other conditions, the pathways leading to pulmonary granuloma formation are less clear. Nevertheless, in all cases of suspected pulmonary granulomatosis it is paramount to exclude infectious causes before considering the rarer, noninfectious reasons for their development, while simultaneously keeping in mind that some of the genetic defects discussed here specifically predispose to infections that lead to the pulmonary granuloma. Certain immunodeficiencies and autoimmune disorders have been classically associated with pulmonary granulomatosis. As the understanding of the genetic basis of many disorders is expanded, so is the possible list of differential diagnoses of pulmonary granulomatosis of genetic origin. Decisive indicators of the underlying disorder can be elicited by pulmonologists, immunologists, rheumatologists, radiologists and pathologists; therefore, a multidisciplinary approach is paramount in correctly diagnosing affected patients.

Early identification of individuals at risk for pulmonary granulomatosis of genetic origin can help to avoid environmental or infectious triggers, support aggressive antimicrobial or anti-inflammatory therapy in patient subgroups and might identify individuals eligible for SCT. A combined diagnostic approach taking clinical presentation, laboratory workup, imaging techniques, histologic findings and genetics results into consideration can therefore help to shape the way to personalised diagnosis and treatment. With the advance of new sequencing techniques, the genetic background of other causes of pulmonary granulomatous inflammation might be discovered in the future.

Previous articles in the Series: No. 1: Daccord C, Good J-M, Morren M-A, et al. Brit-Hogg-Dubé syndrome. _Eur Respir Rev_ 2020; 29: 200042. No. 2: Hadchouel A, Drummond D, Abou Taam R, et al. Alveolar proteinosis of genetic origins. _Eur Respir Rev_ 2020; 29: 200187. No. 3: Cazzato S, Omenetti A, Ravaglia C, et al. Lung involvement in monogenic interferonopathies. _Eur Respir Rev_ 2021; 30: 200001. No. 4: Yokoyama T, Gochuico BR. Hermansky–Pudlak syndrome pulmonary fibrosis: a rare inherited interstitial lung disease. _Eur Respir Rev_ 2021; 30: 200193. No. 5: van Moorsel CHM, Van der Vis JJ, Grutters JC. Genetic disorders of the surfactant system: focus on adult disease. _Eur Respir Rev_ 2021; 30: 200085.
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