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ORIGINAL ARTICLE

Respiratory Complications in Patients with Hyper IgM Syndrome

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Abstract

Purpose Hyper Immunoglobulin M (HIgM) syndrome is a heterogeneous group of primary immunodeficiency disorders, characterized by recurrent infections and associated with decreased serum IgG and IgA, but normal or increased IgM**.** The aim of the present study was to evaluate respiratory manifestations in patients with HIgM syndrome.

Methods A total number of 62 patients, including 46 males and 16 females were included in the present study. To investigate the respiratory complications among HIgM patients, we evaluated the clinical hospital records, immunologic and molecular diagnostic assays, pulmonary function tests (PFT), and high-resolution computed tomography (HRCT) scans.

Results Pneumonia was the most common respiratory manifestation ($n = 35$, 56.4%), followed by otitis media (45.1%), sinusitis (33.8%), and bronchiectasis (14.5%). 52.1% of the patients had abnormal PFT results, with a predominant restrictive pattern of changes. HRCT scans demonstrated abnormal findings in 85.7% of patients with found mutations. Ten cases had hilar lymphadenopathy and para-hilar infiltrates in their HRCT findings. Genetic diagnosis was confirmed in 29 HIgM patients (72.4% CD40 ligand (CD40L) and 24.1% activation-induced cytidine deaminase (AICDA/AID) deficiencies). Majority of patients with CD40L (71.4%) and AID (57.1%) deficiencies had missense mutations. Pneumonia and abnormal high-resolution computed tomography (HRCT) findings were more frequent among patients with CD40L mutation. Respiratory failure constituted the major cause of mortality (37.5%) with majority of cases occurring in CD40L-deficient patients (50%).

Conclusions Respiratory complications are common in patients with HIgM syndrome. A proper awareness of respiratory manifestations in patients with HIgM may result in improved management, reduced morbidity and mortality, and an improvement in the quality of life of the patients.

Keywords Hyper immunoglobulin M · primary immunodeficiency · respiratory complications · pneumonia · otitis media · sinusitis · bronchiectasis

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Introduction

Hyper Immunoglobulin M (HIgM) syndrome (also known as immunoglobulin class switch recombination (CSR) deficiencies) is a group of primary immunodeficiency diseases (PIDs), characterized by increased or normal levels of serum IgM and markedly decreased serum levels of other switched immunoglobulin classes [1–5]. HIgM patients suffer from increased susceptibility to recurrent and chronic infections, immune dysregulation, and malignancies.

Mutations in a number of genes involved in CSR have been implicated in the development of HIgM profile, including CD40 ligand (CD40L), CD40, nuclear factor-kappa-B essential modulator (NEMO/IKKγ), inhibitor of kappa light-chain gene enhancer in B cells, alpha (IκBα), nuclear factor kappa-B subunit 1 (NFKB1), activation-induced cytidine deaminase (AICDA/AID), uracil-DNA glycosylase (UNG), ataxia telangiectasia mutated (ATM), postmeiotic segregation increased 2 (PMS2), MutS Homolog 6 (MSH6), MutS Homolog 2 (MSH2), INO80, the gene-encoding Nibrin/Nijmegen breakage syndrome 1 (NBS1/NBN), meiotic recombination 11-Like Protein A (MRE11), recombination activating gene 2 (RAG2), phosphatidylinositol 3-kinase catalytic delta (PIK3CD), phosphatidylinositol 3-kinase regulatory subunit 1 alpha (PIK3R1), tumor necrosis factor receptor superfamily member 13B (TACI/TNFRSF13B), inducible T-cell costimulator (ICOS), CD19, B cell-activating factor receptor (BAFF-R/TNFRSF13C), LPS responsive beige-like anchor protein (LRBA), phospholipase C gamma-2 (PLCG2), Bruton tyrosine kinase (BTK), and signaling lymphocyte activation molecule-associated protein (SAP) [6–12].

CD40L deficiency leads to increased susceptibility to recurrent chronic infections by encapsulated bacteria and opportunistic infections (e.g., *Pneumocystis jirovecii* (PJP)) [4, 6, 13], while defect in AID results in recurrent chronic infections, caused by encapsulated bacteria [14, 15]. Intravenous immunoglobulin (IVIg) is administered to decrease chronic infections among these patients [16]. Among patients with HIgM, the most frequent clinical manifestations are chronic rhinosinusitis and pulmonary infections such as bronchitis, bronchiectasis, and pneumonia [4, 10, 17]; however, due to immune dysregulation, these patients are also susceptible to non-infectious respiratory complications [18]. Chronic lung disease could be considered a significant source of morbidity and mortality for these patients [19].

However, the information regarding clinical symptoms and radiologic findings in respiratory manifestations in patients with HIgM remains very limited. Therefore, the aim of the present study was to focus on the respiratory complications among Iranian patients diagnosed with HIgM.

Methods

Study Population

The present cohort is a retrospective-prospective study conducted on HIgM patients who were diagnosed and followed up at the Children's Medical Center (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) between 2002 and 2018 [6, 20–24]. Diagnosis of HIgM was based on the diagnostic criteria of ESID (the European Society for Immunodeficiencies) including decreased levels of serum IgG (≤ 2 standard deviations (SD) below normal values for age), normal or elevated serum IgM, exclusion of other hypogammaglobulinemia, and no evidence of profound T-cell deficiency as well as ataxia telangiectasia (https://esid.org/Working-Parties/Registry/Diagnosis-criteria). Molecular diagnoses of patients were performed using a stepwise genetic approach described previously [21, 22]. Due to mortality, lack of consent for the genetic study, and unsolved sequencing data (which have been forwarded for whole genome sequencing), some of patients were not included for the molecular sub-analyses. All of our patients had received regular immunoglobulin replacement therapy (IVIG) promptly after the diagnosis has been made and patients without regular treatment were excluded from this study. This study was approved by the Ethics Committee of the Tehran University of the Medical Sciences and informed consents were obtained from all patients and/or their parents.

Clinical and Imaging Analysis

A two-page questionnaire was designed to obtain all data including demographic information (age at onset of symptoms, age at diagnosis, time to diagnosis), clinical manifestations (first presentation, respiratory complications such as sinusitis, otitis media, pneumonia (recorded by appointed family physicians or chest radiograph admission report), bronchiectasis, non-respiratory complications such as autoimmunity, lymphoproliferative disorders (lymphadenopathy, splenomegaly, hepatomegaly, and granulomatous lesion), chronic diarrhea, oral candidiasis, and meningitis), laboratory data, pulmonary function tests (PFT), and high-resolution computed tomography (HRCT) scans. Respiratory manifestations, the clinical course, and outcome of patients were documented by a primary care physician or pulmonologist before and after the diagnosis of HIgM.

Time to diagnosis was calculated as the time period between the onset of symptoms and the time of clinical diagnosis of HIgM. The duration of follow up was measured as the time between diagnosis and the date of either the last visit or death. Clinical, radiological, and laboratory evidence of lower respiratory tract infections were used to determine the diagnosis of pneumonia based on the Centers for Disease Control criteria

[25]. Sinopulmonary complications were considered sinus disease, allergic rhinitis, rhinorrhea, cough, rhinitis/occasional cough/nasal drip/nasal congestion, chest congestion, sinopulmonary facial swelling, dry cough, otitis media, laryngitis, pharyngitis, pneumonia, empyema, pulmonary abscess, atelectasis, collapse, interstitial lung diseases, asthma, bronchiectasis, and phlegm production.

Given that patients with HIgM are associated with DNA repair defects and are at increased risk of developing malignancy, HRCT scan was only performed only in patients who were medically indicated. Patients with persistent respiratory symptoms for more than 4 weeks underwent HRCT to confirm the presence of chronic lung disease. Each image was assessed to evaluate the presence and severity of different parameters [26–28], using the modified Bhalla scoring method including: (i) the presence and extent of bronchiectasis; (ii) the average severity of bronchial dilatation; (iii) bronchial wall thickness; (iv) the presence or absence of mucus within the large airways, and separately, within the centrilobular bronchioles; (v) the extent of decreased attenuation of the lung parenchyma; (vi) the extent of bronchial wall collapse; and (vii) the extent of tracheal collapse (Table S1).

The definition of mild, moderate, and severe forms of lung involvement was assessed in each lobe of the lung separately by an independent pediatric pulmonologist and radiologist according to a previously published scoring system [29] with evident diagnostic and prognostic advantages in the field of PID [30–33]. Briefly, each lobe was scored separately, and the final score was obtained by summing the total lung scores of two reviewers, with the highest possible score being 25. Bronchiectasis was recognized as bronchial dilatation, associated with thickening of the walls. Bronchial dilatation was noted when the internal diameter of the bronchus was greater than that of the adjacent pulmonary artery. Results were classified as follows: excellent when between 21 and 25 points, good when between 16 and 20 points, mild between 11 and 15 points, moderate between 6 and 10 points, and serious between 0 and 5 points [34].

PFT was performed for patients with 6 years of age and older, according to the American Thoracic Society guidelines [35], using a Jaeger Masterlab Spirometer (Erich Jaeger, Wurzburg, Germany). For each patient, up to three acceptable flow-volume maneuvers were obtained before and 15 min after 400 μg of inhaled salbutamol was administered (metered dose inhaler, MDI). Lung function values were expressed in relation to standard values as a percentage of predicted [36]. A bronchodilator responsiveness was considered positive if forced expiratory volume in the first second (FEV1) was increased equal to or more than 12%. Abnormal lung function was defined by the presence of FEV1, forced vital capacity (FVC), or the ratio between FEV1 and FVC (FEV1/FVC) values below 80% of predicted or forced expiratory flow at 25 to 75% of FVC (FEF25-75%) below 70% of predicted.

Statistical Analysis

Data were analyzed using SPSS 20.0 (SPSS Inc.; Chicago, IL). Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess normality of the data distribution. Parametric analyses were performed on normally distributed data, while non-normally distributed data were analyzed with non-parametric tests. Chi square tests were performed for categorical variables. Kaplan–Meier curves and log-rank tests were used to compare different survival estimates. Statistical significance was defined as $p < 0.05$.

Results

Characteristics of Patients

A total number of 62 HIgM patients (46 males and 16 females) were enrolled in the present study. Table 1 summarizes patients' characteristics. The median (interquartile range, IQR) age of the cohort studied was 9.5 (5.2–18.0) years and the median (IQR) age at the onset of symptoms was 1.0 (0.7–4.0). In 28 patients (45.1%), the initial manifestation occurred before 1 year of age. Only 5 patients were diagnosed later than 16 years of age. The median (IQR) time to diagnosis was 0.7 (0.1–2.9) years and patients were followed for 488 years in total (IQR = 7.0 (4.0–15.0) years). Parental consanguineous marriage was reported in 26 patients (41.9 %) and 6 cases (9.6%) had a positive family history of PID. Among all subjects, 16 patients (25.8%) died during the study period mainly due to respiratory failure ($n = 6$, 37.5%).

Deceased patients had higher prevalence of pneumonia and otitis media compared with survivors; however, this difference was not significant (76.5% vs 52.5%, $p = 0.091$ and 64.7% vs 37.5%, $p = 0.059$, respectively). The median rate of pneumonia and otitis media after HIgM diagnosis was higher among deceased patients compared with survivors (0.39 (0.03–0.71) vs 0.01 (0–0.19) patient year ($p = 0.003$) and 0.10 (0–0.40) vs 0.001 (0–0.11) patient year ($p = 0.029$), respectively). As shown in supplementary Figures S1 and S2**,** there was no statistically significant difference in the overall survival rate among patients with pneumonia ($p = 0.49$) and bronchiectasis ($p = 0.52$).

As shown in Table 2, among all subjects, 29 causative mutations have been identified. Of those, six patients that died (20.6 %) had been diagnosed with CD40L deficiency. Cause of death was available for 4 patients with CD40L mutations, which included pneumonia (3 patients) and hepatic failure in 1 patient. The most common HRCT findings among these subjects were pneumonia followed by bronchiectasis and prebronchial thickening. PJP was isolated in 3 patients. Three of the deceased patients with CD40L deficiency had received hematopoietic stem cell transplantation (HSCT).

Table 1 Comparison of demographic and immunologic data in 62 clinically diagnosed HIgM patients with or without pneumonia during the follow-up period

Parameters	Total ($n = 62$)	With pneumonia ($n = 36$)	Without pneumonia ($n = 26$)	p value
Sex ratio (M/F)	46/16	26/10	20/6	0.55
Consanguinity N (%)	26 (41.9)	16 (45.7)	10 (43.5)	0.86
Alive/dead	38/16	19/12	19/4	0.09
Median age of the cohort studied (year) (IQR)	9.5 (5.2–18.0)	10.0 (6.0–18.5)	7.0 (5.0–15.7)	0.4
Median age at onset of symptoms (year) (IQR)	1.0 (0.7–4.0)	1.0 (0.2–2.7)	1.0 (0.5–4.0)	0.47
Median age at the time of diagnosis (year) (IQR)	2.0 (0.1–5.0)	5.0 (2.0–11.0)	3.0 (1.0–6.5)	0.49
Median time to diagnosis (month) (IQR)	0.7 (0.0–2.9)	2.5 (0.0–6.0)	1.0 (0.0–2.2)	0.06
Median follow-up period; year (IQR)	7.0 (4.0–15.2)	5.0 (4.4–15.0)	6.7 (4.7–13.9)	0.78
IgG (mg/dl) (IQR)	117.0 (45.5–328.0)	100.0 (49.0–230.0)	140.0 (32.0–404.0)	0.38
IgA (mg/dL) (IQR)	10.0 (4.0–21.0)	15.0 (6.0–22.0)	6.0 (2.5–19.0)	0.05
IgM (mg/dL) (IQR)	230.0 (125.0–441)	230.0 (106.0–402.0)	241.0 (160.5–573.0)	0.55
Leukocytes (cells/ μL) (IQR)	11100 (8600–18400)	13700 (9250–18900)	10000 (6775–18407)	0.38
Neutrophils (cells/μL) (IQR)	3724 (1509–5011)	3441 (927–5325)	3736 (1839–5096)	0.42
Lymphocyte (cells/μL) (IQR)	4330 (2640–8747)	4178 (2640–9193)	4402 (2557–8074)	0.96
$CD3^+$ T cell (cells/μL) (IQR)	2728 (1706–6132)	2373 (1450–5995)	3623 (1750–6162)	0.26
$CD4^+$ T cells (cells/μL) (IQR)	918 (606–3979)	895 (547–3667)	1306 (617–4590)	0.42
$CD8^+$ T cells (cells/μL) (IQR)	1366 (736–2186)	1392 (679–2184)	1366 (748–2300)	0.85
$CD16^+$ lymphocytes (cells/μL) (IQR)	962 (392–1827)	459 (292–1827)	1108 (723–2013)	0.29
$CD19^+$ lymphocytes (cells/μL) (IQR)	518 (184–1536)	499 (155–1401)	1071 (374–3326)	0.11

Immunologic and Genetic Findings

IgM levels were elevated in 35 (56.4%) and normal in 27 (43.5%) patients. No abnormalities were found in the levels of $CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$ lymphocyte counts at the time of diagnosis. Eight patients (12.9%) were found to have leukopenia (WBC < 4000 cells/ul). Neutropenia was identified in 10 patients (16.1%, Table 1**)**.

As mentioned previously, genetic evaluation of 29 patients with HIGM phenotype revealed that 21 and 7 patients had mutations in the CD40L and AICDA genes, respectively. Among patients with the CD40L mutations, we found 15 missense, 5 frameshift-nonsense, and 1 splice-site mutation. Among patients with AICDA gene mutations, 4 patients were found to have missense mutations, 2 stop-gain, and 1 splice-site deleterious variants. One patient was diagnosed with NEMO deficiency (Table S2). Among the 29 patients with molecular diagnosis, IgM levels were elevated in 10 (34.4 %) and normal in 24 (82.7 %) patients (Table 2).

Clinical Manifestation

As shown in Fig. 1, respiratory manifestations were the most common initial manifestation among our patients. Prior to the diagnosis of HIgM, the majority of patients ($n = 43$, 69.3 %) experienced at least one episode of acute respiratory infection and 24.1 % ($n = 15$) had experienced pneumonia as the first manifestation of the disease. Four of the 29 HIgM patients with molecular diagnosis (13.7 %) presented with more than one episode of pneumonia prior diagnosis. Sinusitis was documented in 10 monogenic patients (34.4 %) and otitis media was reported in 13 cases during the course of their disease (44.8 %).

The rate of respiratory manifestations before and after the diagnosis is summarized in Table S3. The incidence rate of otitis media was significantly decreased after the diagnosis and initiation of immunoglobulin replacement therapy ($p < 0.05$). The rate of pneumonia and sinusitis were also lower after the diagnosis, but this difference was not significant ($p = 0.5$ and $p = 0.06$, respectively). PJP was diagnosed in three patients.

Ten cases experienced non-infectious respiratory complications mainly due to lymphoproliferative disorders. There were no cases of granulomatous disease, amyloidosis, or respiratory malignancy in our cohort during the follow-up period. In addition to respiratory manifestations, several other affected organs were observed in the HIgM cohort (summarized in Table S4). There was no significant association between respiratory complications and other lymphoproliferative or autoimmune clinical phenotypes (data not shown).

Respiratory Complications

The frequency of respiratory involvement during the course of diseases was 70.3% in our patients. Among HIgM patients who had clinically indicated chest X-ray

Table 2 Comparison of demographic and immunologic data in 29 monogenic HIgM patients with or without pneumonia during the follow-up period

Parameters	Total ($n = 29$)	With pneumonia ($n = 18$)	Without pneumonia ($n = 11$)	p value
Sex ratio (M/F)	27/2	17/1	10/1	0.69
Consanguinity N (%)	13 (44.8)	5 (27.7)	8 (72.7)	0.66
Alive/dead	22/7	12/6	10/1	0.35
Median age of the cohort studied (year) (IQR)	9.0 (4.5–17.0)	9.0 (4.4–20.0)	8.0 (4.4–16.7)	0.87
Median age at onset of symptoms (year) (IQR)	0.6 (0.5–1.2)	7.5 (5.5–12.0)	12.0 (6.0–38.5)	0.43
Median age at the time of diagnosis (year) (IQR)	1.6 (1.0–5.0)	2.2 (1.1–5.1)	1.5 (1.1–5.5)	0.83
Median time to diagnosis (month) (IQR)	0.7 (0.0–2.9)	8.0 (1.7–39.5)	14.0 (0.0–33.0)	0.89
Median follow-up period (year) (IQR)	6.5 (3.8–14.0)	5.0 (4.4–15.0)	6.7 (4.7–13.9)	0.96
IgG (mg/dL) (IQR)	45.5 (5.5–147.5)	62.5 (8.5–151.2)	32.0 (3.5–152.5)	0.58
IgA (mg/dL) (IQR)	8.5 (4.2–21.5)	10.0 (5.7–23.0)	7.0 (3.7–10.7)	0.11
IgM (mg/dL) (IQR)	217.0 (98.0–592.5)	211.5 (79.5–505.7)	268.5 (131.0–744.0)	0.71
Leukocytes (cells/μL) (IQR)	11100 (8600–18400)	13700 (9250–18900)	10000 (6775–18407)	0.38
Neutrophils (cells/μL) (IQR)	3514 (1464–5003)	2997 (859–5137)	3736 (1839–5096)	0.32
Lymphocyte (cells/μL) (IQR)	4161 (2380–8452)	3857 (2380–8806)	4402 (2557–8074)	0.26
$CD3^+$ T cell (cells/μL) (IQR)	5386 (2119–8669)	2259 (1247–5386)	3623 (1750–6162)	0.91
$CD4^+$ T cells (cells/μL) (IQR)	3552 (828–4534)	878 (578–3186)	1306 (617–4590)	0.82
$CD8^+$ T cells (cells/μL) (IQR)	1868 (660–2646)	1235 (649–2180)	1366 (748–2300)	0.51
$CD16^+$ lymphocytes (cells/μL) (IQR)	426 (165–953)	737 (385–1154)	291 (119–415)	0.05
$CD19^+$ lymphocytes (cells/μL) (IQR)	1376 (320–2504)	462 (142–1376)	1071 (374–3326)	0.57

radiography performed, 10 cases (58.8%) had abnormal results including hilar lymphadenopathy and para-hilar infiltrates. PFT was performed on 23 patients with HIgM who were older than 6 years of age and were able to cooperate appropriately. Twelve patients (52.1%) had abnormal PFT results. Among these patients, six cases showed restrictive changes with a FVC% predicted lower than 80%, whereas five patients had obstructive changes of FEV1/FVC less than 70%, and one patient had mixed restrictive and obstructive patterns.

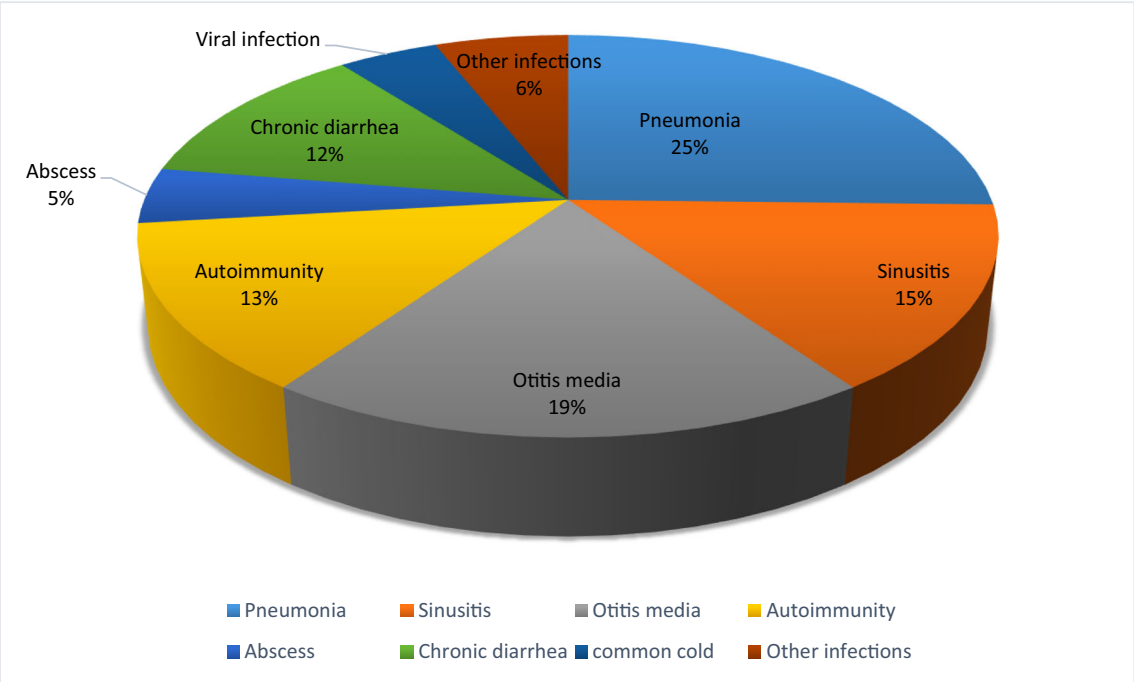

Fig. 1 The frequency of observed various first clinical presentations at the time of disease onset among 29 studied HIgM patients.

During the follow-up period, HRCT was indicated in 23 patients, among 17 (73.9 %) patients had abnormal imaging findings indicative of chronic lung disease (Figs. 2 and 3). Bronchiectasis was the most common radiological finding confirmed in 9 (39.1 %) patients. A pre-bronchial thickening pattern was the main abnormality on HRCT of complicated patients (6 out of 17, 35.2 %). Both bronchiectasis and bronchial wall thickening were mainly found in the left middle lobe. Among 14 patients who died, 5 had abnormal HRCT (3 of them with confirmed CD40L mutation) and 2 had abnormal PFT (1 restrictive and 1 obstructive patterns). The patient with a restrictive pattern in PFT was identified to have CD40L mutation.

The baseline characteristics of HIgM patients who underwent HRCT and were diagnosed with bronchiectasis were different from patients without bronchiectasis. The group of patients with bronchiectasis was older both at the time of onset (3.0 (0.5–12.5) vs 0.5 (0.5–1.0) year, $p = 0.15$) and at the time of diagnosis (13.0 (5–21) vs 1.8 (1.0–5.3) years, $p = 0.03$) compared with patients without bronchiectasis. However, no differences in the number of affected patients and the rate of pneumonia (0.013 vs. 0.05/years, $p = 0.64$) were found among patients with and without bronchiectasis (Table 3).

The Bhalla score quality in our patients is shown in Table S5. Overall Bhalla scores were for 23 HIgM patients that the median of the Bhalla scores for these patients was 15.0 (range 3–25) and only three patients (13.0%) were diagnosed with serious condition scoring. Among 6 patients with bronchiectasis, 3 patients had severe lung involvement in their Bhalla score, while none of the patients without bronchiectasis demonstrated severe lung involvement. The median Bhalla score was significantly lower in patients with bronchiectasis, (8.0 (3.7–14.0)) compared with patients without bronchiectasis (16.0 (12.0–21.0)) ($p = 0.04$, Table 3). A significant inverse correlation was found between the total Bhalla score and age of diagnosis ($r = -0.56$; $p = 0.01$). Bhalla scores were also significantly higher in patients with normal PFT measurements compared with abnormal, although it did not reach significance level (23.5 (17.0–25.0) vs. 10.0 (4.0–21.0), $p = 0.06$). Moreover, there was a significant positive correlation between lymphocyte numbers and Bhalla score ($r = 0.464$; $p = 0.034$). Table S6 summarizes Bhalla score quality for 29 patients with mutation findings.

Respiratory complications were also compared between patients with AID and CD40L deficiencies. Majority of our patients (90.4%) with CD40L mutation did not develop bronchiectasis. On the other hand, 42.8% of patients with AICDA mutation developed bronchiectasis. PFT and HRCT were performed on 9 patients with CD40L mutations. Among the patients with AID deficiency, 3 patients had PFTs done and four required HRCT. Abnormal HRCT findings were observed in 8 patients with CD40L mutation and 3 patients with AID deficiency. Leukopenia (< 4000 cells/ul) and severe neutropenia (< 500 cells/ul) were reported in 2 and 3 patients with CD40L deficiency, respectively, but none of AID deficient patients had hematologic abnormalities. Of note, absolute counts of lymphocytes (8,816.0 vs. 3,429 cells/μL, $p = 0.02$) and neutrophils (1,836 vs. 5,371 cells/μL, $p = 0.01$) were significantly lower in CD40L deficiency. PJP was diagnosed in 3 patients with confirmed CD40L mutation. Other respiratory manifestations and comparative findings are presented in Table 4.

Discussion

HIgM syndrome is associated with increased or normal levels of serum IgM with concomitant low levels of other switched

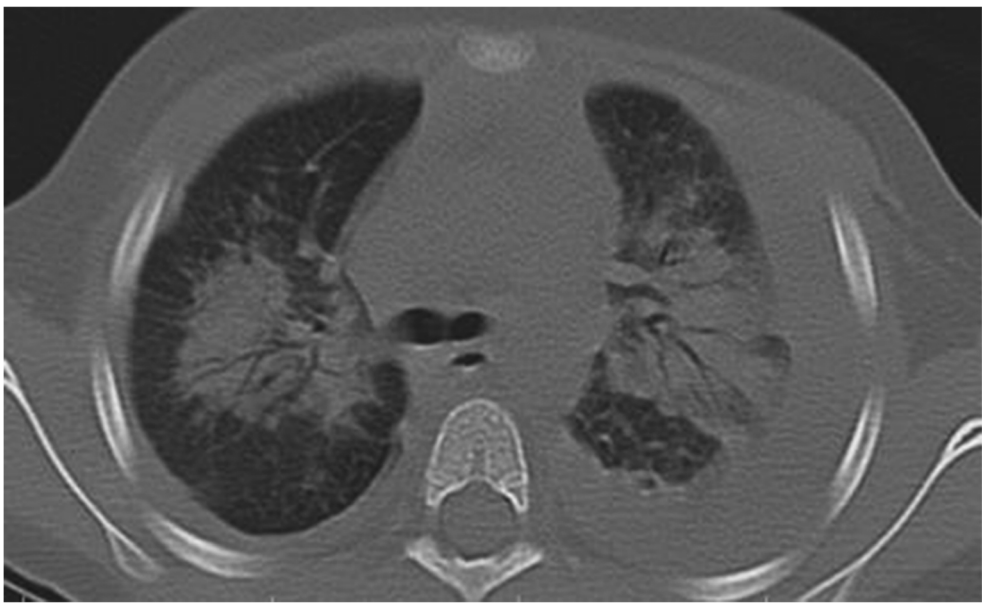

Fig. 2 Thoracic CT of a 17-year-old male due to left pleural effusion and air bronchogram of both lungs.

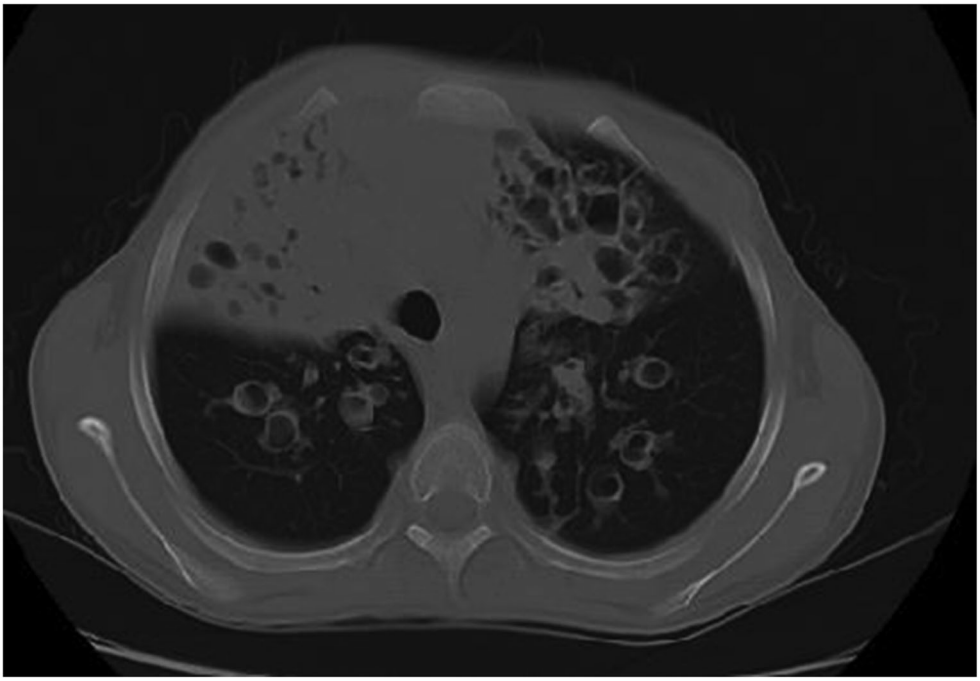

Fig. 3 A 30-year-old male with CD40L deficiency and diagnosed with bilateral bronchiectasis and consolidation in right lung.

immunoglobulin classes leading to a wide spectrum of clinical manifestations, particularly recurrent respiratory tract infections. In the present study, we evaluated respiratory manifestations in HIgM patients by reviewing hospital records, PFT and HRCT results, and the molecular diagnosis.

Our study demonstrated that recurrent upper respiratory infections were the second most common manifestation among patients with HIgM syndrome. Otitis media and sinusitis were seen in 48% and 35% of patients, respectively; which were similar to the rates reported previously [4, 10, 37]. In our cohort, pneumonia was the most common documented presentation among HIgM subjects, with ~60% of the patients experiencing at least one episode of pneumonia before diagnosis. This finding was similar to previous reports in which 63–84% of HIgM patients experienced at least one episode of pneumonia before diagnosis [4, 10, 13, 37, 38]. The mortality rate due to respiratory failure in our cohort was 35.3% which is higher compared with a multicenter study of US Immunodeficiency Network (USIDNET) on 175 HIgM patients with a median age of 12 years old (75% experienced pneumonia) in which only 25% of total mortality were due to respiratory failure [10]. Overall, consistent with prior reports, our results demonstrated that respiratory failure secondary to infection, and in particular pneumonia is the most common cause of death in HIgM patients [19, 20].

In the current study, microbiologic data was only available for patients with complicated pneumonia, who at the time of culture were receiving empiric therapy and prophylactic antibiotic treatment which might have affected the microbiologic assessment. Of note, PJP was isolated as the causative organism of pneumonia in three patients (7.6% of HIgM patients with pneumonia). Although specific causative organism was not recorded in the majority of our patients, encapsulated bacteria have been shown to be the most common pathogens responsible for respiratory infections among patients with HIgM [13]. While not commonly recognized, PJP appears to be quite prevalent in HIgM [4, 13]. In the USIDNET study, 32% of pneumonia cause was associated with PJP which was higher than the rate of *Streptococcus pneumoniae* (17 %) and *Pseudomonas aeruginosa* (15 %). PJP also constitutes 26% of pneumonia causes in Latin America HIgM cohort with 58 patients [10]. Diagnosis of PJP commonly requires broncho-alveolar lavage or lung biopsy, but can be suspected when infiltrates on chest X-ray are associated with the presence of respiratory distress, especially in combination with other clinical and immunologic evidence of HIgM.

The evaluation of lung function by spirometry is as a simple and feasible tool for HIgM patients older than six years. Spirometry was performed in 12 patients in the present cohort and abnormalities were observed in 33% of the patients. Although bronchiectasis was the most common chronic lung disease in this cohort, we observed almost equal rates of restrictive and obstructive patterns, indicating that both restrictive and obstructive patterns can be observed in HIgM patients (probably due to non-infectious complications including inflammatory condition, hypersensitivity or drug-induced reactions, and immune dysregulation affecting lung interstitium [39]). These findings suggest that PFTs are useful for the baseline evaluation and follow-up of respiratory complications in patients with HIgM. Non-infectious respiratory complications were diagnosed in 10 patients (15.6%) of our cohort, which was slightly

Table 3 Comparison of 23 HIgM patients with or without bronchiectasis determined by HRCT

Parameters	With bronchiectasis ($n = 9$)	Without bronchiectasis ($n = 14$)	p value
Demographic data			
Sex (male / female)	7/2	11/3	1.0
Consanguinity (%)	6 (66.7)	10 (71.4)	1.0
Alive/dead	6/3	11/3	0.64
Current age (IQR)	21.0 (12.5–29.5)	9.0 (4.5–16.5)	0.52
Onset age (IQR)	3.0 (0.5–12.5)	0.5 (0.5–1.0)	0.15
Age of diagnosis (IQR)	13.0 (5–21)	1.8 (1.0–5.3)	0.03*
Time to diagnosis (IQR)	4.0 (1–15)	0.8 (0.1–2.6)	0.76
Course of disease (IQR)	14.5 (7.0–25.2)	8.5 (4.5–13.0)	0.04*
Immunologic data			
IgG; (mg/dL) (IQR)	150 (52–450)	46 (11–135)	0.70
IgM (mg/dL) (IQR)	386 (131–838)	223 (78–351)	0.13
IgA (mg/dL) (IQR)	10 (2–23)	9 (4–15)	0.25
Leukocytes (cells/μL) (IQR)	7100 (5100–9000)	11020 (9132–18900)	0.30
Lymphocytes (cells/μL) (IQR)	2385 (1377–4500)	7634 (4550–12616)	0.27
$CD3^+$ T cell (cells/μL) (IQR)	1764 (691–6364)	5197 (2250–8662)	1.0
$CD4^+$ T cells (cells/μL) (IQR)	810 (254–3901)	3451 (813–4478)	1.0
$CD8^+$ T cells (cells/μL) (IQR)	691 (298–2034)	1658 (620–3113)	0.43
$CD16^+$ lymphocytes (cells/μL) (IQR)	530 (212–925)	905 (535–1740)	0.30
$CD19^+$ lymphocytes (cells/μL) (IQR)	261 (115–1292)	1405 (512–2693)	0.68
Respiratory complications			
Otitis (%)	7 (77.8)	5 (35.7)	0.08
Pneumonia (%)	7 (77.8)	8 (57.1)	0.39
Sinusitis (%)	6 (66.7)	5 (35.7)	1.0
PFT (%)	4 (44.4)	12 (85.7)	0.06
Obstructive	1	1	
Restrictive	2	2	
PFT value			
PEF	57.5 (45.5–87.5)	81.0 (60.5–93.0)	0.37
FEV1	60.5 (46.7–90.0)	92.0 (75.0–96.5)	0.25
FEV1/FVC	81.5 (78.5–85.2)	86.3 (80.5–90.5)	0.21
MEF 25-75	58.5 (46.7–75.5)	69.5 (38.0–92.5)	0.73
Other HRCT complication (%)	6 (66.6)	11 (78.7)	0.64
Hilar or mediastinal lymphadenopathy	0	4	
Air trapping	0	1	
Consolidation	3	2	
Nodule	0	1	
Septal thickening	1	2	
Infiltration	0	1	
Atelectasis	2	2	
Bhalla score (IQR)	8.0 (3.7–14.0)	16.0 (12.0–21.0)	0.04*

PFT, pulmonary function testing, *HRCT*, high-resolution computed tomography; *IQR*, interquartile range with 75^{th} and 25^{th} percentiles; *PEF*, peak expiratory flow; *FEV1*, forced expiratory volume; *FVC*, forced volume vital capacity; *MEF*, maximal expiratory flow

*p value is statistically significant, < 0.05

higher than the rate reported by USIDNET (12%) and Latin America (10.3%) cohorts [10, 37].

HRCT imaging for patients with PAD emerges as an essential approach in evaluating respiratory complications due to its high sensitivity in detecting anatomic lesions in the respiratory tract. Since chest X-ray sensitivity for diagnosis of early respiratory pathologies in patients with HIgM is low, HRCT should be considered in all patients with chronic respiratory

Table 4 Comparison of respiratory complications between patients with CD40L and AICDA mutations

Parameters	CD40L deficiency $N = 21$	AID deficiency $N = 7$	p value*
Dead/alive	7/14	0/7	0.29
Onset age (IQR)	1.0 (1.0–1.0)	5.0 (1.0–14.5)	0.038*
Age of diagnosis (IQR)	1.5 (1.0–4.7)	8.0 (6.5–15.0)	0.007*
Time to diagnosis (IQR)	0.5 (0.0–2.0)	3.0 (0.5–6.0)	0.181
Respiratory manifestations (%)			
Otitis	8 (61.9)	4 (57.1)	0.223
Sinusitis	6 (28.6)	3 (42.8)	0.335
Pneumonia	14 (66.7)	3 (42.8)	0.464
PFT findings (%)			
Normal	7 (33.3)	1 (14.2)	0.12
Abnormal	2 (22.2)	2 (42.8)	
PFT values			
PEF	86.0 (76.2–95.5)	47.0 (46.1–51.3)	0.221
FEV1	95.5 (84.7–97.7)	66.0 (44.0–66.0)	0.153
FEV1/FVC	86.0 (83.0–92.2)	84.0 (78.0–86.4)	0.352
MEF 25-75	77.0 (45.7–97.7)	46.0 (33.0–49.3)	0.152
Presence of bronchiectasis (%)	3 (14.2)	2 (28.5)	0.155
CT scan findings (%)			
Normal	1 (11.1)	1 (14.2)	0.538
Abnormal	8 (88.9)	3 (42.8)	
Bronchiectasis	2 (22.2)	3 (42.8)	
Bhalla score (± SD)	17.00 ± 4.03	12.00 ± 9.05	0.141
Bhalla quality			
Serious		1 (14.2)	0.113
Moderate		2 (42.8)	
Mild	4 (44.4)		
Good	3 (33.3)		
Excellent	2 (22.2)	1 (14.2)	

PF, pulmonary function testing; *HRCT*, high–resolution computed tomography; *SD,* standard deviation

*p value < 0.05 is statistically significant

The between-group comparison was made using Mann–Whitney's U test

symptoms to monitor the disease progression [40, 41]. In the present study, abnormalities were found in the majority of patients with HIgM who underwent HRCT imaging, indicating the importance of this modality for diagnosis and monitoring of respiratory complications. There is a debate about performing routine HRCT in all patients with CSR defects (due to DNA repair defect and the risk of tumorigenesis) [42]; however, our finding emphasizes that HRCT should be considered an imaging modality of choice in HIgM cases with clinical indication. Furthermore, in our cohort, no malignancy was detected during the follow-up after HRCT. Bronchiectasis was found in 28% of our HIgM patients. This rate is similar to other cohorts of patients with PAD [43–45].

In a recent review of more than 900 patients with non-cystic fibrosis bronchiectasis, PID was the cause of bronchiectasis in 16% of patients [46]. These findings indicate the importance of infection control in these patients to prevent the irreversible lung damage and bronchiectasis. Our results show that patients with a longer time to diagnosis had significantly higher rates of bronchiectasis. Previous reports suggested that appropriate treatment with immunoglobulins and antibiotics may delay the development and alter the natural course of bronchiectasis [47]. Moreover, earlier initiation of IVIg therapy reduces the probability of developing chronic lung disease and decreases frequency and severity of infections [48]. Delay in the diagnosis of HIgM results in considerable morbidity (due to recurrent pneumonias) which may result in structural lung damage and bronchiectasis [49]. The presence of bronchiectasis at the time of diagnosis among PID patients was also shown to be a predictor of poor prognosis and higher mortality [50]. Thus, earlier diagnosis and initiation of appropriate treatment can prevent the development of chronic lung disease resulting in a significant improvement in the quality of life and prognosis of this group of patients.

Among our patients, genetic evaluation led to an identification of a causative mutation in 29 patients, of which 21 and 7 patients had mutations in the CD40L and AICDA genes, respectively. Apart from mutations in CD40L and AICDA genes in one patient (NEMO deficiency), we identified a missense mutation in the nuclear factor-kappa B essential modulator mutation. Mutations in the gene-encoding NEMO have been previously reported [51]. Most reported mutations in HIgM patients are related to CD40L and AID; thus, identifying mutations in *NEMO* gene carries a special significance and indicates that a diagnosis of NEMO deficiency should be considered in patients who are negative for mutations in the genes of HIgM.

Comparative analysis of 28 patients with underlying mutations in CD40L and with AICDA did not reveal any significant differences in the rate respiratory infections or PFT/HRCT findings. To date, there are no studies evaluating respiratory complications based on PFT and HRCT results in HIgM patients with known genetic defects. Only one report from Latin America survey showed a higher occurrence of pneumonia and upper respiratory tract infections in AID-deficient patients compared with CD40L-deficient group; however, they did not have a comparative analyze on PFT and HRCT results [37]. We observed an increased rate of pneumonia and a higher abnormal HRCT scan finding in patients with CD40L mutation compared with patients with AICDA mutations. However, abnormal PFT and bronchiectasis were more common in patients with AID deficiency. Moreover, moderate and serious Bhalla scores were more often documented in AID-deficient patients. Since patients with CD40L mutations are associated with cellular immune defects as well as neutropenia, more severe respiratory symptoms may present in earlier stages in this group compared with patients with AID mutations.

Our finding that patients with CD40L mutations underwent radiologic evaluations such as CT scan early in the course of disease further supports the notion that this group of patients may have earlier and more serious presentations compared with the patients with mutations in AID mutations. Conversely, among our 7 patients with AID mutation, we observed longer times to diagnosis as they had gradual onset of respiratory manifestations. We believe that this delay in diagnosis, ultimately led to a higher rate of non-infectious pulmonary complications in these patients, supported by an observed trend towards higher rate of abnormal PFT measurements and bronchiectasis, compared with the CD40L group. Of note, we also report a higher frequency of lymphoproliferative manifestations in patients with CD40L deficiency, a phenomenon which has been recently reported in another study [52].

The main limitation of the present study was the relatively small sample size of our cohort, which may have reduced the power to detect a significant correlation between respiratory complications and mutation diagnosis. Additionally, radiological examination such as HRCT scan was only performed for 23 out of 62 patients. Finally, the efficacy of antibiotic prophylaxis was not evaluated in this study due to inherent inability to accurately record all the antibiotics taken by the patients stemming from wide availability of over the counter antibiotics in Iran. Future studies may be required to investigate the efficacy of immunoglobulin replacement therapy on PFT measures and pulmonary complications in HIgM patients.

Conclusions

Our data indicates that the respiratory system is the most commonly affected in patients with HIgM syndrome. The results highlight the importance of early surveillance in HIgM patients by better identification of infectious and non-infectious respiratory complications. This group of patients requires regular visits accompanied by appropriate tests including PFT and HRCT imaging to diagnose respiratory pathologies in earlier stages and also for the monitoring of already existing abnormalities. Improved awareness of respiratory complications in patients with HIgM could lead to accelerated timing of diagnosis and improves the prognosis of these patients.

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Compliance with Ethical Standards This study was approved by the Ethics Committee of the Tehran University of the Medical Sciences and informed consents were obtained from all patients and/or their parents.

Conflict of Interest The authors declare that they have no conflict of interest.

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