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PHYSICIAN CONNECT

Dear Doctor,

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This issue contains:

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Best Regards,

Medical Team, Micro Labs Limited.

1. Identification of potential key genes in idiopathic pulmonary fibrosis and their relationship with immune cells

Introduction:

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease that causes fibrosis, inflammation, and damage to lung architecture. It was believed that aberrant wound healing and damage to the alveolar epithelium play a major role in the development of this disease. An estimated 5.6 people per 100,000 were predicted to have IPF annually; around 70% of patients were male and have a history of cigarette smoking. Although the exact causes of IPF are still unclear, a mix of environmental and genetic factors are considered to be responsible.[1] Also, IPF's pathophysiology remains unknown, however it was thought to be caused by repeated injury and deregulation of alveolar epithelial cells. The majority of patient's experience delayed diagnoses, as a result of the gradual onset of interstitial lung diseases (ILDs), the difficulty of imaging and histology to differentiate IPF from other common ILDs, and the lack of dependable laboratory tests. Due to a delayed diagnosis and limited available treatments, the median survival period for those with IPF was two to five years and had a thirty percent five-year survival rate, less than many malignancies. There are currently no effective therapy options for IPF. The only two suggested medications for IPF that have been approved were pirfenidone and niedanib; nevertheless, they were only able to delay the disease's progression and not reverse its reduction in lung function.[2] The purpose of this study was to use integrated bioinformatics analysis to identify potential critical genes in IPF and their link to immune cells.

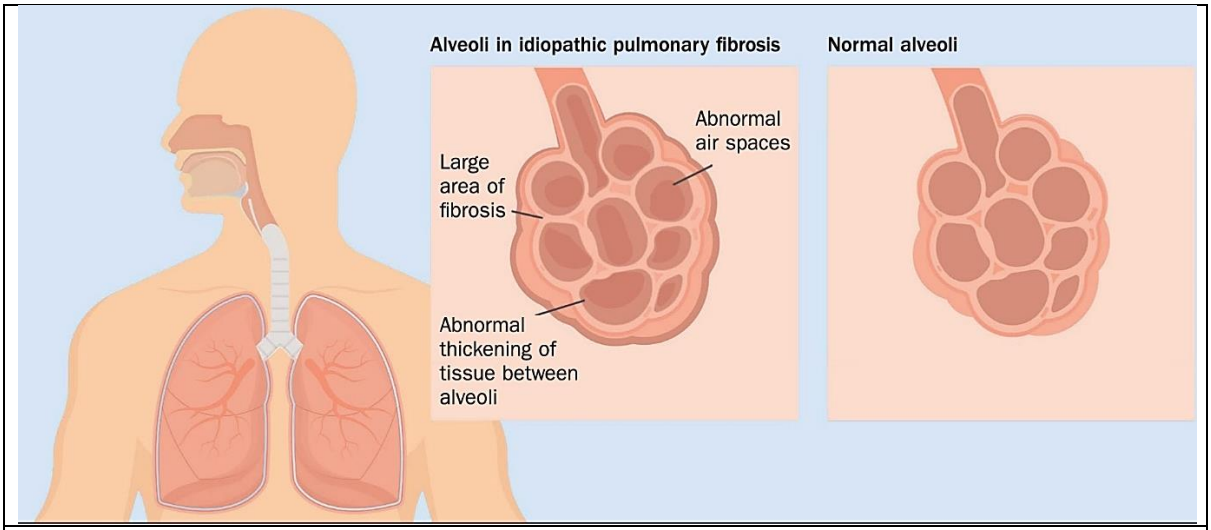

Fig 1. Idiopathic pulmonary fibrosis

Methods:

Gene microarray data were gathered from the Gene Expression Omnibus (GEO) to analyze differential expression. This study identified differentially expressed genes (DEGs) and conducted functional enrichment analysis. This study used three machine learning methods to identify genes linked to idiopathic pulmonary fibrosis (IPF). The diagnostic importance and

putative co-regulators were discussed. This study used single-sample gene set enrichment analysis (ssGSEA) to investigate the link between important genes and immune infiltrating cells. Subsequently, single-cell RNA sequencing (scRNA-seq) was performed to identify cell types that expressed important genes in IPF samples. In vivo and in vitro investigations were used to validate candidate gene expression using western blot (WB), quantitative real-time PCR (qRT-PCR), and immunohistochemistry (IHC).

Results:

Based on two datasets, 647 DEGs of IPF were found, comprising 422 upregulated and 225 downregulated genes. They were linked to biological processes such cell migration, structural organization, immune cell chemotaxis, and extracellular matrix. Three machine learning methods identified CFH and FHL2 as essential genes for accurately diagnosing IPF. Using ssGSEA, both CFH and FHL2 were found to be significantly associated with several immune cells, including B and NK cells. ScRNA-seq research revealed that CFH and FHL2 were elevated in human IPF tissues, as confirmed by in vitro and in vivo investigations. According to a gene multifactor regulatory network, 98 miRNAs, 2 lncRNAs, and 34 TFs were all involved in the regulation of FHL2, whereas CFH was controlled by a total of 18 miRNAs and 7 TFs. Interestingly, the regulatory network showed that TFs co-regulate two important genes, RAD21, LMNB1, FOXA2, FOXA1, SPI1, and CTCF (Fig 2).

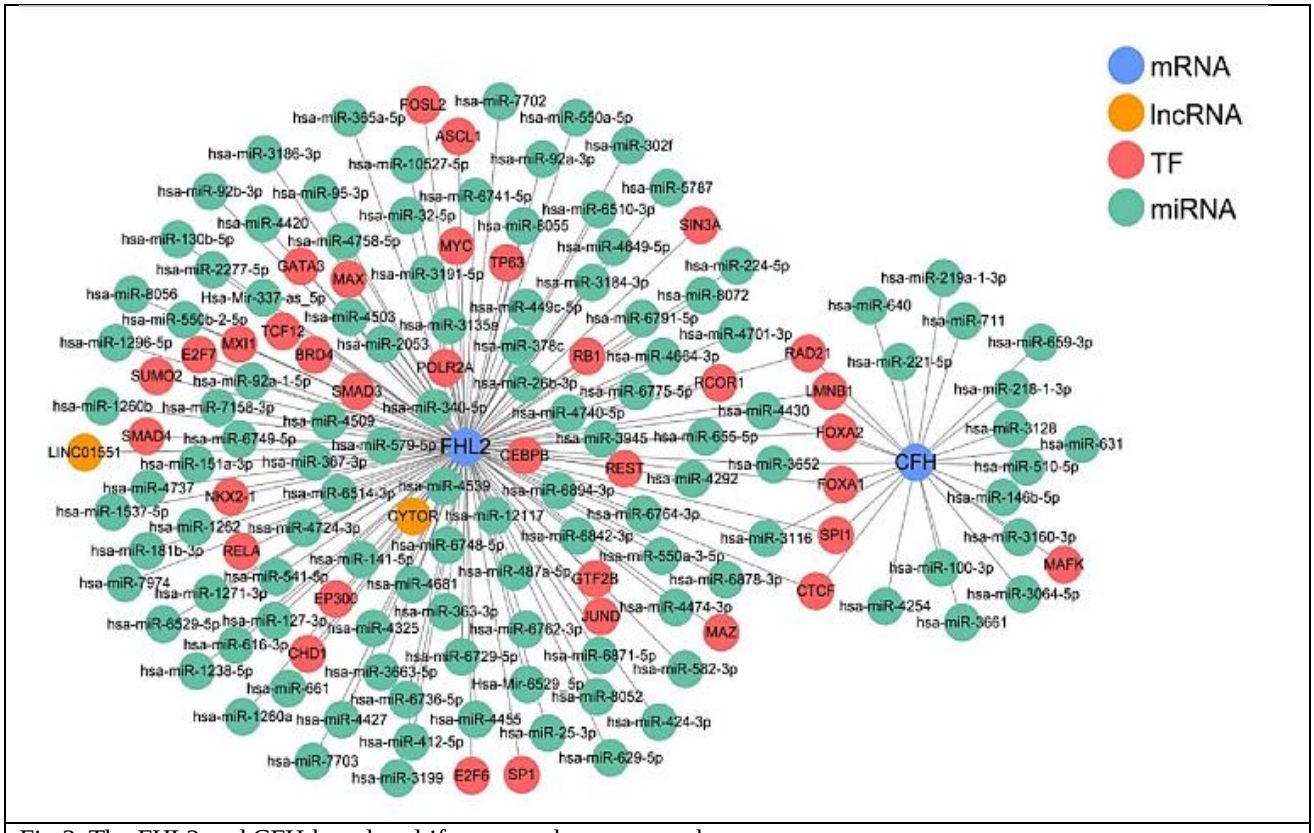

Fig 2. The FHL2 and CFH-based multifactor regulatory network

Discussion:

This study analyzed the gene transcriptome of IPF patients and healthy persons using bioinformatics. Results revealed 422 up-regulated DEGs and 225 down-regulated DEGs.[2] ACTA2 and COL1A1 were considered the primary indicators of pathological fibrosis in IPF.[3] However, the diagnostic specificity was restricted as they can be expressed in normal cells such smooth muscle cells and pericytes, as well as pathogenic fibroblasts that overproduce extracellular matrix.[4] In this study, elevation of CFH and FHL2 in the IPF group was mostly seen in fibroblasts. This suggested that these molecules can accurately identify IPF fibroblast foci.[2]

Conclusion:

This study identified CFH and FHL2 as possible biomarkers for IPF, which might be used in clinical applications. Further research into the role of these genes in IPF and their interactions with immune cells will help better understand the disease's pathophysiology and identify potential treatment options.

The results of the study resulted in the identification of two new possible biomarkers for IPF: CFH and FHL2. These indicators may be useful for diagnosis in upcoming clinical settings.

Reference:

1. Glass DS, Grossfeld D, Renna HA, Agarwala P, Spiegler P, DeLeon J, Reiss AB. Idiopathic pulmonary fibrosis: Current and future treatment. The clinical respiratory journal. 2022 Feb;16(2):84-96.
2. Liu X, Yang M, Li J, Liu H, Dong Y, Zheng J, Huang Y. Identification of CFH and FHL2 as biomarkers for idiopathic pulmonary fibrosis. Frontiers in Medicine. 2024 May 9;11:1363643.
3. Bai X, Zhao G, Chen Q, Li Z, Gao M, Ho W, Xu X, Zhang XQ. Inhaled siRNA nanoparticles targeting *IL11* inhibit lung fibrosis and improve pulmonary function post-bleomycin challenge. Sci Adv. 2022 Jun 24;8(25):eabn7162.
4. Tsukui T, Sun KH, Wetter JB, Wilson-Kanamori JR, Hazelwood LA, Henderson NC, Adams TS, Schupp JC, Poli SD, Rosas IO, Kaminski N, Matthay MA, Wolters PJ, Sheppard D. Collagen-producing lung cell atlas identifies multiple subsets with distinct localization and relevance to fibrosis. Nat Commun. 2020 Apr 21;11(1):1920.

2. Accuracy of Cardiopulmonary exercise test for detecting inadequate stroke volume (SV) augmentation during exercise

Introduction:

Cardiopulmonary exercise testing (CPET) is a thorough examination of physiologic responses to exercise and cardiorespiratory fitness that includes gas exchange analysis during maximum activity. The direct non-invasive measurement of minute ventilation, heart rate, and expired gases analysis at rest and during exercise, as opposed to exercise electrocardiogram (ECG), yields precise and repeatable data on the relationship between ventilation, gas exchange, and cardiovascular and musculoskeletal function. It also makes it possible to identify deviations from normal.[1] In individuals experiencing dyspnea and exercise intolerance following an acute pulmonary embolism (PE), CPET has been suggested as a non-invasive means of identifying pulmonary vascular disease. The primary sign of cardiac limitations linked to pulmonary vascular disease was insufficient stroke volume (SV) augmentation during exercise. More than half of patients with dyspnea following PE had indications of insufficient SV augmentation, according to CPET. CPET results indicating pathologically reduced SV augmentation, however, have never been confirmed using the gold standard of direct assessment in pulmonary vascular disease patients by right heart catheterization (RHC). The simultaneous measurement of oxygen consumption rate (VO2), mixed venous O2 content, arterial O2 content, and heart rate were necessary for the "direct Fick method" of determining SV by RHC.[2] This study examined the efficacy of CPET in identifying insufficient SV augmentation during exercise, a critical indicator of cardiac dysfunction in pulmonary vascular disease patients.

Methods:

This retrospective analysis examined individuals with suspected pulmonary vascular disease who had CPET and RHC measures at rest and anaerobic threshold (AT). This study compared CPET-determined $O2{\cdot}pulse_{AT}/O2{\cdot}pulse_{rest}$ to RHC-determined SV_{AT}/SV_{rest} and assessed its sensitivity and specificity for detecting SV_{AT}/SV_{rest} below the lower limit of normal (LLN). Similar analyses were conducted in this study to compare SV_{AT}/SV_{rest} with peak tricuspid regurgitant velocity (TRV_{peak}), which was determined echocardiographically.

Results:

Eighty-three simultaneous RHC and CPT tests were conducted during the research period. Thirty-six tests were included in the study after meeting the inclusion criteria. There were 25 (69.4%) women and 11 (30.6%) males present. There were co-existing cardiopulmonary comorbidities in 12 individuals (33.3%). Thirty-six studies recorded SV and O_2 pulse both at rest and during AT. While TRV_{peak} did not show a strong correlation with SV_{AT}/SV_{rest} (r = -0.09, 95% CI -0.47, 0.33; p = 0.69), $O2{\cdot}pulse_{AT}/O2{\cdot}pulse_{rest}$ did (r = 0.72, 95% CI 0.52, 0.85;

p<0.0001). Compared to TRV_{peak} (0.69, SE 0.10; p=0.12), O_2 ·$pulse_{AT}$ /O2·$pulse_{rest}$ (0.92, SE 0.04; p=0.0002) had a considerably better AUROC to identify SV_{AT} /SV_{rest} below the LLN (Fig 1). For insufficient SV_{AT} /SV_{rest}, O_2·$pulse_{AT}$/O_2·$pulse_{rest}$ of less than 2.6 was 92.6% sensitive (95% CI 76.6%, 98.7%) and 66.7% specific (95% CI 35.2%, 87.9%).

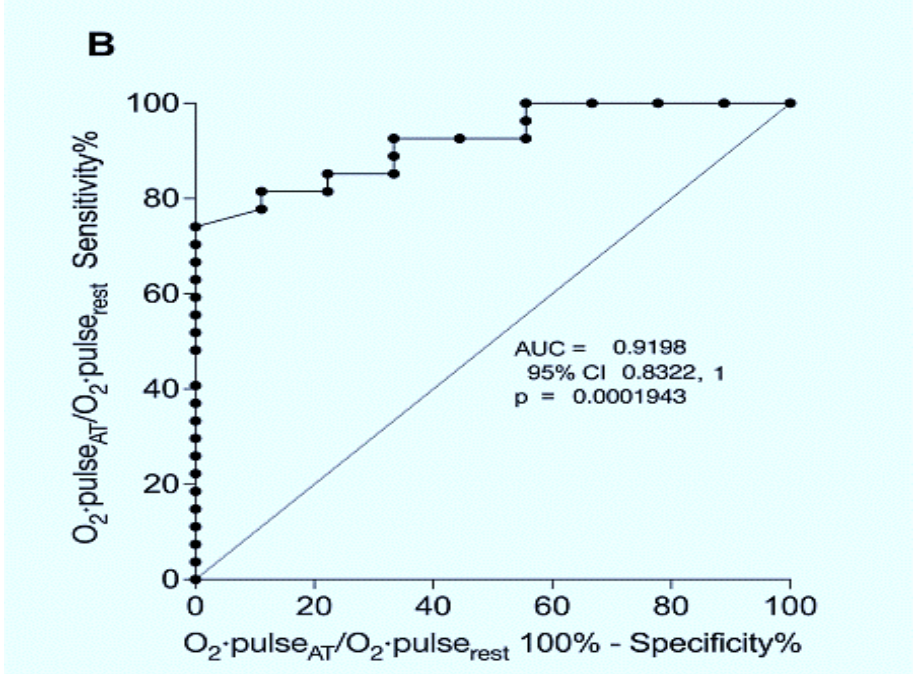

Fig 1. The area under the ROC curve (AUC) for O2·$pulse_{AT}$/O2·$pulse_{rest}$ to identify SVA_{AT} below the lower limit of normal (LLN)

Discussion:

This study demonstrated the accuracy of O_2·$pulse_{AT}$/O2·$pulse_{rest}$ in predicting SV_{AT}/SV_{rest} in a sequential series of patients undergoing combined CPET and RHC for clinical assessment of dyspnea likely linked to pulmonary vascular disease. Validation of the accuracy of O_2·$pulse_{AT}$/O_2·$pulse_{rest}$ indicated that SV augmentation makes CPET a useful and informative non-invasive technique that may be used to help identify between deconditioning or anxiety and pulmonary vascular disease of the several individuals experiencing dyspnea following pulmonary embolism.[2] Low O_2·$pulse_{AT}$/O_2·$pulse_{rest}$, which was assessed noninvasively during CPET, in patients with symptomatic post-pulmonary embolism showed insufficient SV augmentation due to persistent pulmonary vascular occlusion.[3]

Conclusion:

Compared to echocardiography, CPET was more accurate in identifying inadequate SV augmentation. For non-invasive screening of individuals at risk for pulmonary vascular disease, such as those who have prolonged dyspnea following a pulmonary embolism, CPET-determined O_2·$pulse_{AT}$ /O2·$pulse_{rest}$ may play a significant role.

The accuracy of CPET in diagnosing insufficient SV augmentation was higher than that of echocardiography.

Reference:

1. Glaab T, Taube C. Practical guide to cardiopulmonary exercise testing in adults. Respiratory research. 2022 Jan 12;23(1):9.
2. Alotaibi M, Yang JZ, Papamatheakis DG, McGuire WC, Fernandes TM, Morris TA. Cardiopulmonary exercise test to detect cardiac dysfunction from pulmonary vascular disease. Respir Res. 2024 Mar 11;25(1):121.
3. Fernandes TM, Alotaibi M, Strozza DM, et al. Dyspnea Postpulmonary Embolism from physiological Dead Space Proportion and Stroke volume defects during Exercise. Chest. 2020;157(4):936–44.

3. Comparison of the effectiveness of three commonly prescribed oral antidiabetic drugs added to metformin for people with type 2 diabetes mellitus requiring second line treatment

Introduction:

Type 2 Diabetes Mellitus (T2DM) is defined by persistently high blood glucose levels or an increase following carbohydrate-rich meals. Unlike Type 1 Diabetes, which was defined by insulin insufficiency, patients with T2DM often have higher insulin levels (fasting and/or after glucose administration), unless there was beta cell failure.[1] Type 2 diabetes mellitus affects 463 million individuals globally (9. 3%).This was a progressive condition that affects most people and carries a risk of many consequences, such as chronic renal disease and cardiovascular disease (CVD). According to a recent study examining second-line treatments for type 2 diabetes mellitus across 38 countries, the most often prescribed oral medications were sodium-glucose cotransporter-2 (SGLT-2) inhibitors (8.3%), sulfonylureas (40.9%), and dipeptidyl peptidase-4 (DPP-4) inhibitors (48.3%). Among these oral therapies, SGLT-2 inhibitors are a relatively recent and expensive class of medications.[2] The purpose of this research was to evaluate the efficacy of three orally administered, frequently prescribed antidiabetic medications when combined with metformin in patients with type 2 diabetes mellitus who needed second line therapy in normal clinical practice.

Methods:

In this Cohort study, 75739 individuals with type 2 diabetes mellitus who started using metformin together with a sulfonylurea, DPP-4 inhibitor, or SGLT-2 inhibitor as their second line oral antidiabetic therapy were included. The primary outcome was the absolute difference in glycated haemoglobin A_{1c} (HbA_{1c}) between the initial reading and the follow-up after a year. Secondary outcomes included time to ≥40% decline in eGFR, major adverse kidney event, hospital admission for heart failure, major adverse cardiovascular event (MACE), and all-cause mortality. Systolic blood pressure, body mass index (BMI), and estimated glomerular filtration rate (eGFR) were measured at one and two years. Additionally, changes in HbA1c were noted at that time.

Results:

In the study, 75739 individuals with type 2 diabetes mellitus who started using SGLT-2 inhibitors, DPP-4 inhibitors, or sulfonylureas as second line oral antidiabetic therapy were included. Of them, in addition to metformin, 25693 (33.9%) started therapy with sulfonylureas, 34464 (45.5%) with DPP-4 inhibitors, and 15582 (20.6%) with SGLT-2 inhibitors. Between baseline and a year later, SGLT-2 inhibitors were more successful in lowering mean HbA1c levels than DPP-4 inhibitors or sulfonylureas. Among individuals having observed follow-up measurements, those taken sulfonylureas had the highest change in mean HbA1c level from baseline to one year (-18 mmol/mol), compared with DPP4 inhibitors (-10 mmol/mol) and SGLT-2 inhibitors (-14 mmol/mol) (Fig 1). The reduction of BMI and systolic blood pressure was more successful with SGLT-2 inhibitors than with sulfonylureas or DPP-4 inhibitors. When SGLT-2 inhibitors were compared to DPP-4 inhibitors (0.32, 0.12 to 0.90) and sulfonylureas (0.46, 0.20 to 1.05), the risk of hospital admission for heart failure was lower.

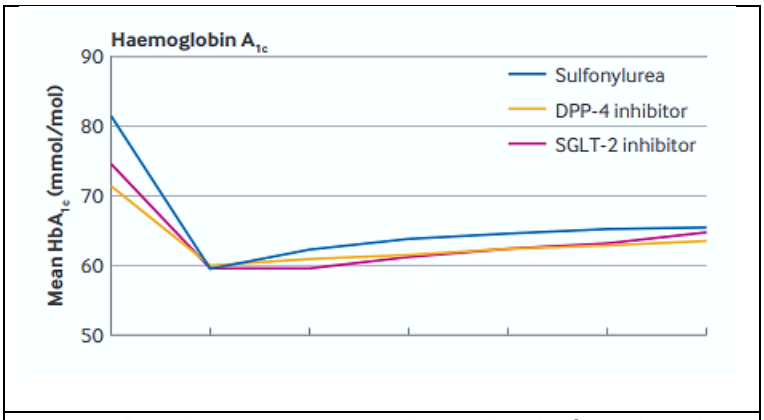

Fig 1. The change in mean HbA1c levels from baseline to one year follow-up.

Discussion:

After reducing the risk of confounding using an instrumental variable analysis, this study found that second-line treatment with SGLT-2 inhibitors for people with type 2 diabetes mellitus was more effective than sulfonylureas or DPP-4 inhibitors in reducing mean HbA1c levels, BMI, and systolic blood pressure in this comparative effectiveness study. This study showed that SGLT-2 inhibitors protect against heart failure compared to DPP-4 inhibitors. This was similar to previous study and showed that SGLT2i and GLP1RA were linked to a decreased risk for several cardio-renal end points when taken in addition to metformin in individuals with type 2 diabetes.[3]

Conclusion:

In this target trial emulation study, SGLT-2 inhibitors were found to be superior to DPP-4 inhibitors or sulfonylureas in lowering mean HbA1c, BMI, and systolic blood pressure. They

were also found to be less likely to cause hospital admission for heart failure (compared with DPP-4 inhibitors) and kidney disease progression (compared with sulfonylureas), with no significant variations in other clinical endpoints.

In terms of reducing mean HbA1c, BMI, and systolic blood pressure, SGLT-2 inhibitors were shown to be more effective than DPP-4 inhibitors or sulfonylureas.

Reference:

1. Westman EC. Type 2 Diabetes Mellitus: A Pathophysiologic Perspective. Front Nutr. 2021 Aug 10;8:707371.
2. Bidulka P, Lugo-Palacios DG, Carroll O, et al. Comparative effectiveness of second line oral antidiabetic treatments among people with type 2 diabetes mellitus: emulation of a target trial using routinely collected health data. BMJ. 2024 May 8;385:e077097.
3. Sim R, Chong CW, Loganadan NK, et al. Comparative effectiveness of cardiovascular, renal and safety outcomes of second-line antidiabetic drugs use in people with type 2 diabetes: A systematic review and network meta-analysis of randomised controlled trials. Diabet Med. 2022 Mar;39(3):e14780.

4. Case Report on Amyloid Goiter due to Behcet's Disease

Introduction:

Amyloidoses are uncommon and heterogeneous disorders that cause aberrant protein accumulation in tissues. Based on electron microscopy, amyloid fibrils are non-branching, hard, and have a diameter of 8–12 nm.[1] Large amounts of amyloid deposition in the thyroid gland can cause an enlarged gland called an amyloid goiter; it can result from either primary or secondary amyloidoses. Thyroid function tests are frequently non-specifically changed in amyloid goiter patients, and most of them are clinically euthyroid. Despite the fact that amyloid protein is frequently deposited in the thyroid gland, amyloid goiter is an uncommon medical condition that is typically not identified prior to surgery.[2] This was a case report of a 42-year-old male patient whose Behcet's illness resulted in a secondary amyloidosis diagnosis.

Case presentation:

A 42-year-old male patient presented to the hospital with a little enlarged right thyroid gland since 2016. Since 2005, the patient has been identified as having Behcet's illness. It was made more difficult by secondary amyloidosis, which resulted in nephrotic syndrome, chronic renal failure, and the eventual need for kidney transplantation in 2010. Neck ultrasonography (US) showed an enlarged, heterogeneous thyroid gland with no nodules. The findings of the fine needle aspiration (FNA) biopsy were "in keeping with goitrous nodule, no evidence of malignancy." According to the patient's laboratory results, he has subclinical hyperthyroidism. As a result, he took 40 mg of thiamazole daily and followed up with an endocrinologist. The patient was well until 2022, when he began to complain of hoarseness, dysphagia, and dyspnea due to a thyroid gland that grown quickly. Upon physical examination, the front part of the neck showed signs of swelling. Upon palpation, there was a solid, multinodular swelling on both sides that was not painful and did not reach the retrosternal region. The thyroid function tests, complete blood count, and serum electrolytes were unremarkable. However, phosphorus levels were slightly decreased, and kidney function tests were slightly elevated. The BUN was normal, and creatinine was 1.52 mg/dl (range 0.6-1.2 mg/dl). A neck computed tomography (CT) scan performed in August 2022 without contrast revealed a noticeably enlarged heterogeneous thyroid gland. It spread inferiorly to the manubrium sterni, encircling the trachea without compression or mass effect and encircling the common carotid arteries bilaterally without a clear invasion. It reached the level of the bilateral

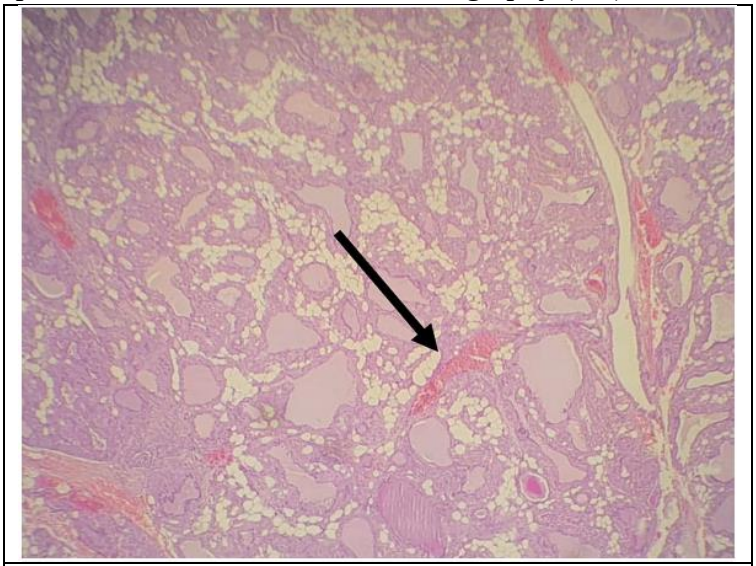

Fig 1. Deposits of homogeneous, eosinophilic, amorphous substances in thyroid tissue

submandibular glands superiorly. On the neck US, there was lateral deviation of the main neck arteries and bilateral expansion of the thyroid lobes with a lobulated outline that extended to the thoracic inlet.

Flexible fiberoptic laryngoscopy revealed normal laryngeal architecture and vocal cord movement, with no evidence of disease. The patient then had a complete thyroidectomy; however, during the procedure, one of the parathyroid glands was accidentally removed and later found its way back into the patient's left neck muscles. Laryngeal nerves were not damaged. On the third postoperative day, the patient was discharged from the hospital after an uncomplicated postoperative stay. The thyroid gland was around 14 × 10 × 5 cm and was visible as grayish tissue. Step sectioning exposed a surface with a fleshy incision. Histopathology revealed thyroid tissue with amorphous eosinophilic fibrillary material in the perifollicular and perivascular regions, replacing thyroid follicles in certain locations (Figure 1) and fatty metaplasia foci (Figure 2).

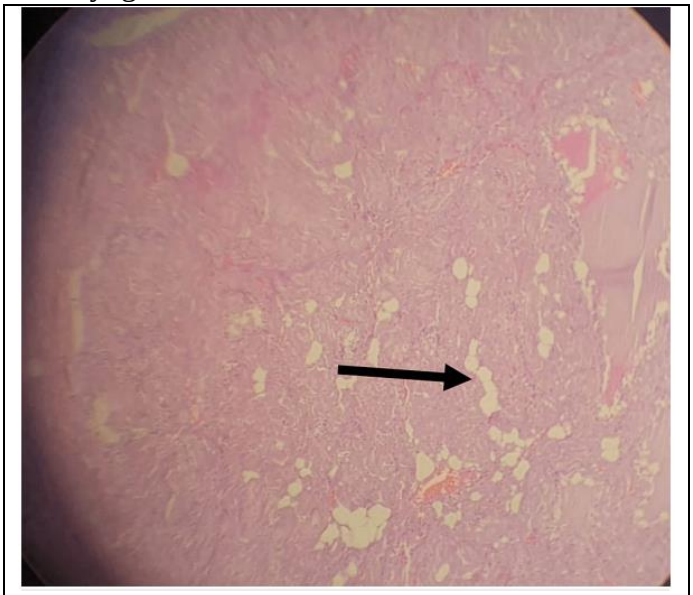

Fig 2. Thyroid gland fatty metaplasia

Discussion:

Amyloidosis is a condition caused by the accumulation of insoluble amyloid proteins in many organs, limiting their function. The FNA biopsy method was frequently employed for assessing lesions of the thyroid. When amyloid goiter was detected, FNA biopsy could provide samples for histopathological analysis. In the present case, the FNA biopsy was crucial in ruling out cancer and directing future diagnostic and therapeutic approaches. Amyloid goiter can be characterized by an uneven pink amorphous material.[2] However, in the previous case on colloid amyloid, FNA reveal solid hyaline-like substance. About 10–40% of FNAs in amyloid goiter only showed abnormal follicular cells. Histopathology was required to determine the exact diagnosis of amyloid goiter. Amyloid proteins were deposited in amyloidosis histological samples, and these proteins may be selectively stained with Congo Red. This stain displayed a distinctive apple-green birefringence under polarized light, which was thought to be a reliable indicator of the presence of amyloid.[3]

Conclusion:

Amyloid goiter is an uncommon condition that requires a high level of suspicion in individuals with rapidly growing thyroid glands and a history of persistent inflammation. A FNA biopsy need to be carried out to rule out thyroid cancer. A histological study was performed postoperatively to determine a final diagnosis.

Amyloid goiter is an uncommon, however individuals with rapidly expanding thyroid glands and a history of chronic inflammatory illness should have a high level of suspicion. An FNA biopsy need to be carried out to rule out thyroid cancer.

References:

1. Picken MM. The pathology of amyloidosis in classification: a review. Acta haematologica. 2020 Jul 30;143(4):322-34.
2. Khader A, Abed RN, Rabee AR, Ayasa LA, Khrishi RH, Judeh KA, Janazreh MJ, Ibrahim DO. Amyloid Goiter Secondary to Behcet's Disease: A Case Report and Literature Review. Cureus. 2023 Nov 29;15(11): e49650.
3. Orrego JJ, Chorny JA. Amyloid goiter as the first recognizable manifestation of immunoglobulin light chain amyloidosis. AACE Clin Case Rep. 2019 Jun 26;5(5): e326-e329.