Revisit of an old way

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The two cases

A 67-year-old lady with history of GOLD stage IV COPD, history of right pneumothorax in 2012 and two episodes of left pneumothorax with chemical pleurodesis done in 2018. She presented to the Emergency department of a regional hospital in 10th June 2019 for dyspnea and chest pain. She was diagnosed to have left pneumothorax and chest drain was inserted. However, she developed extensive surgical emphysema and the left pneumothorax persisted after 2 weeks. A second chest drain insertion was refused by patient and she was then discharged with as-needed oxygen therapy.

She first presented to our hospital 1 month later in mid-July for persistent dyspnea. Chest radiograph confirmed the presence of persistent left pneumothorax. An argyle chest drain was inserted under ultrasound guidance. Since there was no improvement after 1 week, a CT was performed which showed a large pneumothorax with midline shift and the chest drain was traversing left lower lobe parenchyma. Her argyle chest drain was replaced with a Seldinger chest drain but there was persistent left lower zone loculated pneumothorax and continuous bubbling on chest drain. We have consulted the cardiothoracic surgeon and they suggested not for surgery. Bronchoscopy was done for assessing feasibility of EBV insertion in mid-Aug but failed to identify the leakage site. Another CT was performed which revealed new left loculated hydropneumothorax with mild mediastinal shift and the chest drain traversed left lower lobe parenchyma. CT guided pigtail catheter insertion was performed in early Sept and we have performed minocycline twice in late-Sept but the air leak failed to stop. Autologous blood pleurodesis was performed in early Oct and her chest drain was blocked on the next day hence it was removed. Serial CXR monitoring showed static small left loculated pneumothorax and she was discharged on day 6 after pleurodesis. Subsequent follow-up over 3 months showed only a very small rim of loculated left pneumothorax and her short-term oxygen could be weaned off.

The second case was a 70-year-old gentleman with history of GOLD stage III COPD. He presented with dyspnea and chest pain in late-Oct and the CXR on admission showed a large pneumothorax. A chest drain was inserted at the Emergency Department. Unfortunately, there was persistent pneumothorax and air leak at 2 weeks after admission. Cardiothoracic surgeon was consulted, and they advised us that he was not a surgical candidate. In view of slow progress at 3rd week, a CT was arranged which showed a large non-tension right hydropneumothorax with chest drain in-situ. EBV insertion was performed and a total of 3 EBV were inserted. Balloon occlusion testing showed immediate stopping of the air leak, and three EBV were inserted at the right upper lobe bronchi. At roughly 20 hours after EBV insertion, he developed ipsilateral tension pneumothorax with right lower lobe collapse. His chest drain was immediately replaced but there was still persistent air leak despite drainage. Autologous blood pleurodesis was performed on day 6 of the second chest drain insertion. Bubbling stopped within 2 days and chest drain was taken off on day 4 after blood pleurodesis. He has no recurrence for 4 months and the EBV was removed.

Treatment on persistent air leak

We have presented two cases of persistent air leak that failed conventional treatment and they were successfully treated by autologous blood pleurodesis. We would like to review the current evidence of treatment on persistent air leak due to spontaneous pneumothorax with the main focus on autologous blood patch pleurodesis (ABPP).

Surgical pleurodesis was found to have a high successful rate on persistent air leak. Pleurodesis (Either mechanical abrasion or chemical pleurodesis) can be done via VATS or medical thoracoscopy. When combined with blebectomy or bullectomy, the recurrence rate was found to be less than 5%[1-4]. However, many of the patients are not surgical candidates and they will need other measures to control their air leak.

Chemical pleurodesis has been commonly used. Usual agents include graded talc and tetracycline derivative. They have relatively low recurrent rate with studies quoting 3.3%-12% for talc[5-9] and 0%-25% for tetracycline derivative[5, 10-11]. However, they have a number of adverse effects. Talc is well known to be causing pain (31%)[12], fever (13%-63%)[12-13], acute lung injury (2.8-5.6%)[14] and empyema. It can rarely cause adult respiratory distress syndrome (1%)[15-16]. Tetracycline can cause pain and fever (74-91%)[5, 13] but major complication is uncommon[5]. For chemical pleurodesis to be successful, it has to be performed in a fully re-expanded lung with no residual air space.

Bronchoscopic interventions are also possible options. Endobronchial intrabronchial valves can be inserted via bronchoscopy. One study[17] has found it to be effective with 47.5% of patient had complete resolution of air leak and 45% had a reduction of air leak. The mean valve insertion to chest tube removal was 21 days. However, local data from our centre[18] has revealed only a successful rate of only 22%. Case selection is also very important as an intact interlobar fissure on CT scan and immediate and complete air leak cessation after EBV placement were found to be the necessary but not sufficient factor for successful outcome.

Autologous blood patch pleurodesis

Autologous blood patch pleurodesis (ABPP) is not a new method to control persistent air leak. It was first described by Robinson CL. in 1987 for the treatment of 25 patients with chronic spontaneous pneumothorax[19] with a success rate of 85%. Only 4% of patient suffered from empyema. It was subsequently described as a last resort for patient with persistent air leak after lung resection[20] but it was often not the first line treatment in persistent air leak. Recent studies has shown an increasing role of ABPP in managing persistent air leak.

Mechanism

It is proposed that it has dual mechanisms[21-26]. The direct mechanical action of fibrin due to direct sealing of the leak with hematoma makes immediate cessation of air leak possible. The presence of blood also induces adhesions between the visceral and parietal pleura due to inflammation. Whereas in chemical pleurodesis, it only produces inflammation and scarring but no 'patch' effect[13]. Therefore the time taken to pleurodesis will be shorter with ABPP in theory[13]. There is an animal study that compared talc, doxycycline with blood on the effect of macroscopic adhesion and microscopic inflammation[27]. It was found that talc and doxycycline produced more macroscopic adhesion and microscopic inflammation than blood although blood also produce more microscopic inflammation than chest tube control alone. This may suggest that the effect of autologous blood patch is more likely to be a physical phenomenon rather than chemical pleurodesis.

Efficacy of ABPP

There has been a lot of debates on the efficacy of ABPP, it is more studied in post–surgical patients. There were two prospective small-scale study[23, 28] showing excellent results, with air leak stopped in 70% of patients in 12 hours and in all patients in 24 and 48 hours. There were two larger retrospective studies showing promising results with air leak stopped within 12 hours in 81% and within 24 hours in 100% of patients[21]. The overall successful rate was 85% with mean time to termination of air leak of 1.5 days only[29]. It was also shown that the efficacy was not affected by the type of surgery and the underlying disease[30].

The evidence for spontaneous pneumothorax is more limited but there are new studies published recently. The largest prospective case control series was conducted in Turkey from 1993-1996 involving 167 cases with primary or secondary spontaneous pneumothorax[22]. Thirty two patients undergone blood pleurodesis while 135 patients received drainage only. It showed that air leak ceased within 72hr in 84% after pleurodesis and the duration of air leak was significantly shorter than in simple drainage. There was no recurrence of pneumothorax in ABPP group (0 vs 22) during 12-48 months of observation. It was also well tolerated without the use of analgesia or sedation. Only 9.4% of patient suffered from empyema and they all responded to drainage and antibiotic.

There was another prospective case series in 1994-1997 conducted in Japan with 17 episodes of secondary spontaneous pneumothorax with persistent air leak of more than 5 days[25]. It reported a successful rate of 59% and there were only 2 cases of recurrence at 8 days and 5 months which were treated successfully by repeated blood pleurodesis. There was no harmful effect observed and no sedation or anti-pyretic was needed. It was also found that with repeated pleurodesis there were still successful cases despite initial failure.

A recently published RCT conducted in Egypt, involving a total of 48 patients also showed promising results[31]. 26.1% of patient required 1 attempt of blood pleurodesis, 52.2% required 2 attempts and 21.7% required 3 attempts in order to have the air leak stopped. Whereas for the control group who only received blood pleurodesis after 10 days of conservative treatment, only 33% of patient had the air leak stopped without the need of pleurodesis. Majority required one or two blood pleurodesis as salvage therapy. It was also found that blood pleurodesis can lead to a shorter day to air leak seal off (5.43 vs 10.54) and duration of chest drain kept in patient (7.87 vs 12.79) compared to control group. The overall success rate was 78.3% compared to 8.33% in control group. The overall complications rate was comparable between two groups and they were mainly fever and pleural infection.

There was a prospective study of 50 patients comparing talc, tetracycline and autologous blood[13]. The success rate as defined by air leak stopped by 72 hours was 75% for autologous blood, 84% for talc and 64% for tetracycline. The air leak termination time was shortest for autologous blood (27.2 hours) and significantly longer for talc (51 hours) and tetracycline (64 hours). There was only 1 case of empyema in autologous blood group which responded to antibiotic. Talc and tetracycline group were associated with more side effects, including fever, pain, hypotension, SVT, convulsion and ARDS. It had also shown that the VC, FVC and FEV1 were significant lower at 1 and 3 months after treatment in talc and tetracycline than in autologous blood group.

For specific disease groups, there were studies for the efficacy on PAL in patient with ILD and ARDS. In a retrospective review conducted in Kyoto in 2011[32], it was found that the cure rate of autologous blood pleurodesis was comparable to that of chemical pleurodesis (72.7% vs 78.6%) in patient with ILD. The time to recurrence after air leak cessation was also longer in autologous blood pleurodesis than in chemical pleurodesis (39.5 days vs 26 days).

The study concluded that the efficacy of blood pleurodesis is comparable to chemical pleurodesis and is worth considering as a first line treatment for PTX secondary to ILD. There was also a prospective case control study on patient with ARDS conducted in 2006[33] which found that blood pleurodesis group had a significantly lower death rate, shorter weaning time than control group, less patient requiring tracheostomy and less hemodynamic instability.

In summary, ABPP has shown to facilitate early air leak termination. It is at least as efficacious as talc or tetracycline with a low recurrence rate. It can also facilitate early chest drain removal and a shorter hospital stay. It has the advantage of being able to be performed in patient with residual air space. Lung function test does not seem to be affected by ABPP. It may be particularly useful in specific groups of patients including interstitial lung diseases or ARDS.

Optimize the strategies for ABPP

There are some on-going debates on how to optimize the strategies for ABPP.

1. Amount of blood to be instilled.
2. Timing of ABPP.
3. Number of treatments required.
4. Technique of ABPP.

The most discussed issue is the amount of blood instilled. Some authors suggested to use 50ml to reduce chance of empyema[13, 23, 30] as blood is an ideal medium for bacteria and drain will likely colonized with bacteria while others suggested to use a single high dose (100–150 ml[21, 24, 26] or 2ml/kg[35]) for a better efficacy. As of today there is still no consensus on the optimal amount of blood and further studies are needed to determine the optimal dosage.

With regards to the timing of ABPP, it was shown that it could be done as early as 3 days[31] and when the lung is not yet re-expanded[25]. Whereas in chemical pleurodesis, it is usually only effective when the lung has fully re-expanded. This is likely due to the difference in mechanism between ABPP and chemical pleurodesis. It was also noted in one study that a trend toward greater immediate success when instillation is performed earlier[36].

Multiple studies have shown positive results in repeated procedures if initial attempt has failed[19-20, 25]. Repeated blood pleurodesis achieved 94% and 97% success rate in 24 hours and 48 hours respectively[37] with some even reported up to 100%[21]. Some studies proposed if the air leak is not stopped within 48 hours, a further dose should be administered[21, 37].

Most studies recommend to use 10-20ml normal saline flush after instillation of blood.

There was one author recommend using 20ml air flush rather than saline flush as saline will dilute the blood which reduce the chance of pleurodesis[38]. No other studies has suggested to use air instead of saline.

Previous study on tetracycline showed minimal difference to distribution of radiolabelled tetracycline when there is a complex pleural space[39]. One author proposed that as blood clots within minutes, rotation would seem inappropriate and there will be increased risk of displacement of chest tube[40]. However many other authors advocate rotation to achieve a homogeneous distribution of blood[31, 35]. Its usefulness was not well investigated in other studies.

Complication

ABPP is usually well tolerated. It has been described as a painless procedure and no sedation or analgesic is needed[21-22, 25, 28]. The most common adverse events is transient fever (9 -13%)[22, 24, 28, 38] and pleural effusion (8-28%)[22, 24, 38]. Empyema is uncommon (0%-9%)[22, 24, 28, 38].

There was one case report of tension pneumothorax[41] which the chest drain became non-functional after repeated blood patch pleurodesis and the obstruction was only cleared by forcibly injecting 50ml normal saline into the chest tube.

The author made the following recommendations:

1. Autologous "blood patching" should be performed through large bore catheters.
2. Venesection should be performed using 50ml syringes from an intravenous cannula (18 gauge) in an upper limb vein with rapid transfer of blood into the chest drain.
3. Chest drain catheter should be flushed with normal saline after each injection of blood, a 50 ml normal saline flush should be ready in case of chest drain obstruction.
4. Resuscitation equipment should be ready and operator should be experienced in the management of tension pneumothorax with large bore cannulae and emergency chest drain insertion.

Conclusion

In conclusion, blood pleurodesis is an old method that was used in controlling air leak three decades ago. Recent studies have shown that it is at least as effective as the traditional chemical pleurodesis on primary or secondary spontaneous pneumothorax. It is safe and well tolerated, major complication is uncommon. It has the advantages of being able to be performed in patient without a full re-expanded lung and being a painless procedure which doesn't required analgesia. It has the potential to become the first line treatment in patients with interstitial lung diseases or ARDS. For those who failed traditional chemical pleurodesis or the lung failed to expand, blood pleurodesis is worth attempting, especially if EBV is not possible.

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Rare association of aromatase inhibitor and Sjögren's Syndrome: A case report

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Introduction

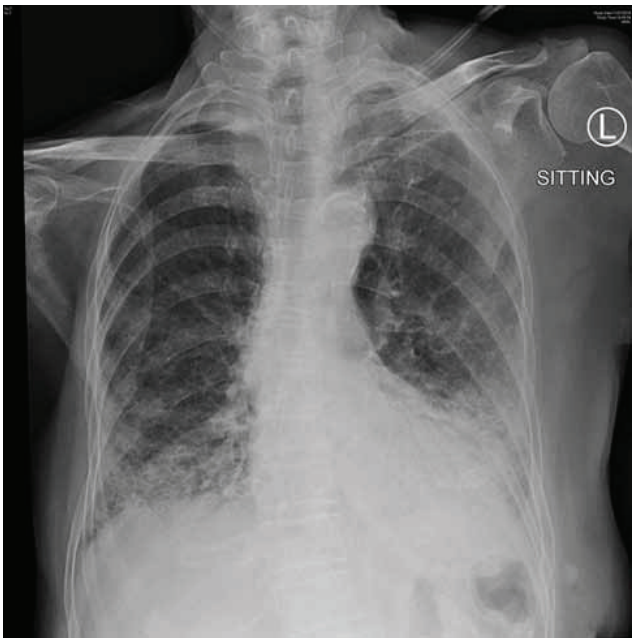
Breast cancer is the commonest cancer among females in Hong Kong; the number of newly diagnosed cases has increased by 3.8 times from 1,152 in 1993 to 4,373 in 2017[1]. Since its approval in 1998, tamoxifen has been used to treat hormone-receptor-positive breast cancer. Third-generation aromatase inhibitors (AIs) have now surpassed tamoxifen as first-line therapy for postmenopausal women with metastatic, hormone receptor-positive, breast cancer. Side effects of AIs are mainly related to their impact on bone mineral density, lipid profile, cardiovascular system, and musculoskeletal symptoms, with few case reports on AI induced autoimmune disorders[2-9]. Here we describe a case of AI associated Sjögren's Syndrome (SjS) with dry eyes, probable dry mouth, interstitial lung disease and raised autoimmune markers.

Case

A 78-year-old housewife who was a non-smoker was admitted in July 2019 for non-productive cough and breathlessness for 2 months. She had a history of right mastectomy for breast cancer, followed by chemoradiotherapy in mainland China in 1996. There was relapse at the left supraclavicular lymph node soon after the patient refused to take Tamoxifen in 2000. Progesterone had been tried for 6 months. Due to weight gain, Letrozole (2.5mg daily), an aromatase inhibitor, had been used since November 2001. Her other past medical history included sinus tachycardia, hypertension, high cholesterol and reflux oesophagitis. Her usual medications were Aspirin, Imdur®, Metoprolol, Pantoprazole, Simvastatin, Calcium and Letrozole.

On admission, the patient was afebrile and her oxygen saturation on room air was 96%. There were bilateral fine basal crepitation on auscultation, and Chest X-ray (CXR) showed bilateral lower zone infiltrates **(Figure 1)**. Blood tests showed mild leukocytosis (10.97 x 109/L), anemia (10.8g/L), elevated inflammatory markers (ESR 120mm/hr, CRP 26mg/L) as well as increased globulin level (58g/L). The liver and renal function tests were all normal (urea 4.6mmol/L, Creatinine 73umol/L, bilirubin 8umol/L ALP 59U/L, ALT 9U/L), as well as urinalysis. The patient was initially treated with antibiotics (Intravenous Augmentin 1.2 g q8h and then sulperazone 1 g Q12h) for suspected community-acquired pneumonia. Yet there were no improvements in symptoms and imaging. Microbiological workups including nasopharyngeal aspirate for respiratory virus PCR and culture, sputum for bacteria and acid fast bacilli smear and culture were all negative.

Figure 1. CXR on admission

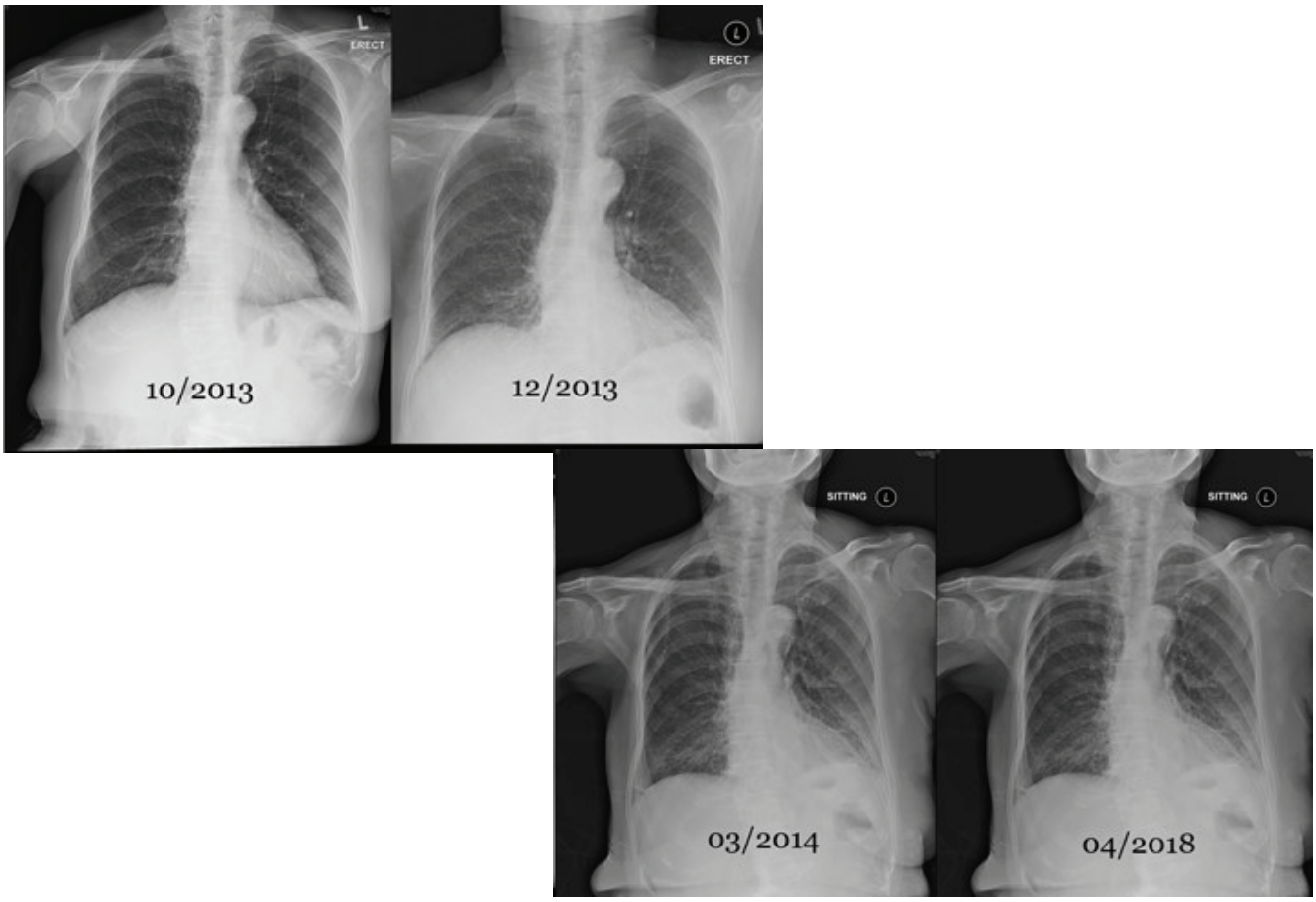


The respiratory team was consulted. Review of records showed that the patient was first seen at the medical clinic in 2007 for palpitations. No apparent cause for her sinus tachycardia (~100-120/minute) could be found all along and holter in 2011 did not show any arrhythmia. However, abnormalities in blood tests had been noted since presentation viz. raised ESR and globulin **(Table 1)**. Workup for multiple myeloma was negative. In September 2011, she had an admission for severe choking after snacking. On arrival, her oxygen saturation was as low as 47%. After discharge, her choking symptom persisted for around one month. In May 2012, the patient started to have complaints of dry eyes. She also had complaints of arthralgia: severe low back pain due to scoliosis and degenerative changes (since 2011), right wrist pain (in March 2013), right metatarsal phalangeal joint pain (in May 2013) and lower rib cage pain (since September 2013). The lower zone reticular shadows on CXR could first be detected in December 2013 with progression over the years **(Figure 2)**.

Table 1. Table of blood tests

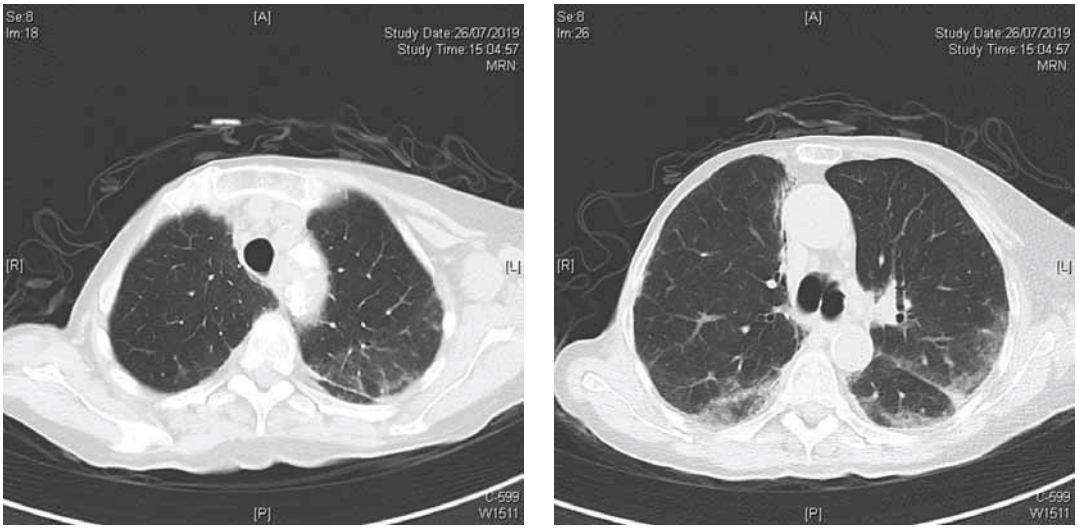
	04/2008	05/2010	09/2011	07/2012	12/2013	01/2014	01/2015	10/2017	04/2018	07/2019
Protein (64-81g/L)	83↑	91↑		86↑	80	89↑	95↑	102↑	106↑	85↑
Albumin (35-52g/L)	39	35		34↓	29↓	33↓	35	36	36	27↓
Globulin (25-39g/L)	44↑	56↑		52↑	51↑	56↑	60↑	66↑	70↑	58↑
Urea (2.6-6.6mmol/L)	5.5	4.9	3.9	5.2	3.7	4.6	5.2	5.6	15.2↑	4.6
Creatinine (49-83umol/L)	71	86	73	74	73	81	81	89↑	163↑	73
WBC (3.7-9.2 x10^9/L)	9.2	8.8	7.7	8.4			15.7↑	7.22	8.08	10.97↑
HGB (11.7-14.9g/dL)	12.7	14.4	12.3	12.3			12.8	12.2	11.4↓	10.8↓
PLT (145-370 x10^9/L)	386↑	321	284	200			273	302	263	560↑
ESR (<37mm/hr)		53↑	62↑	64↑						120↑
CRP (<5mg/L)			7.3	3.2						26↑

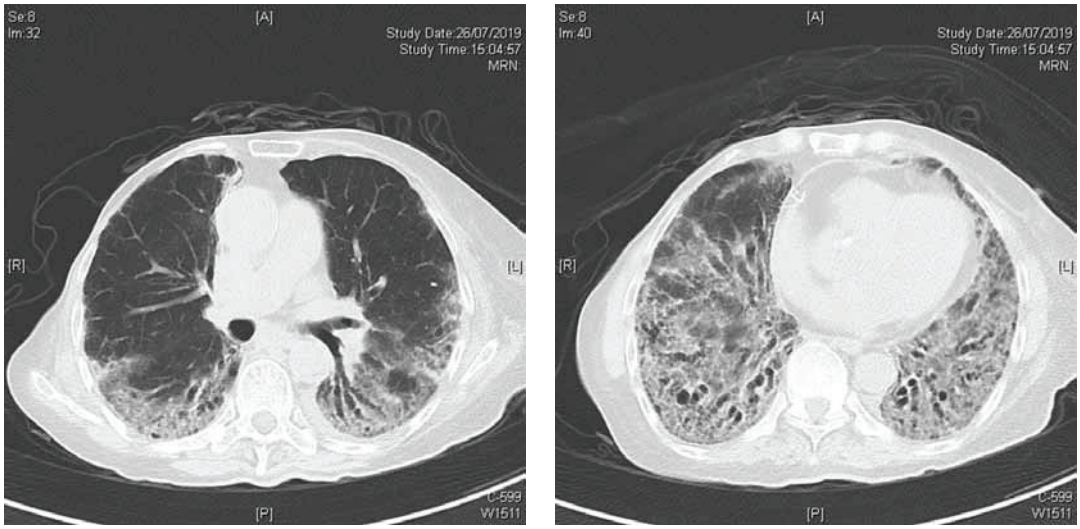
Figure 2. Previous CXRs



An autoimmune cause of interstitial lung disease (ILD) was thus suspected and multiple work-up were done. Ophthalmology consultation was made. Signs of exposure keratopathy including punctate epithelial erosions were found. There was decreased tear breakdown time signifying decreased tear production. Lung function test was arranged but the patient failed to perform. High-resolution CT (HRCT) of the thorax showed thickening of interlobular septa and ground glass opacities with honeycombing appearance in both lungs **(Figures 3a-d)**. CT of paranasal sinus showed symmetrical and unremarkable parotid glands, with no obvious focal mass lesion or significant lymphadenopathy at the levels included. Bronchoscopy was performed and bronchial aspirate for acid fast bacilli culture and cytology were negative. Transbronchial

Figure 3a-d. HRCT

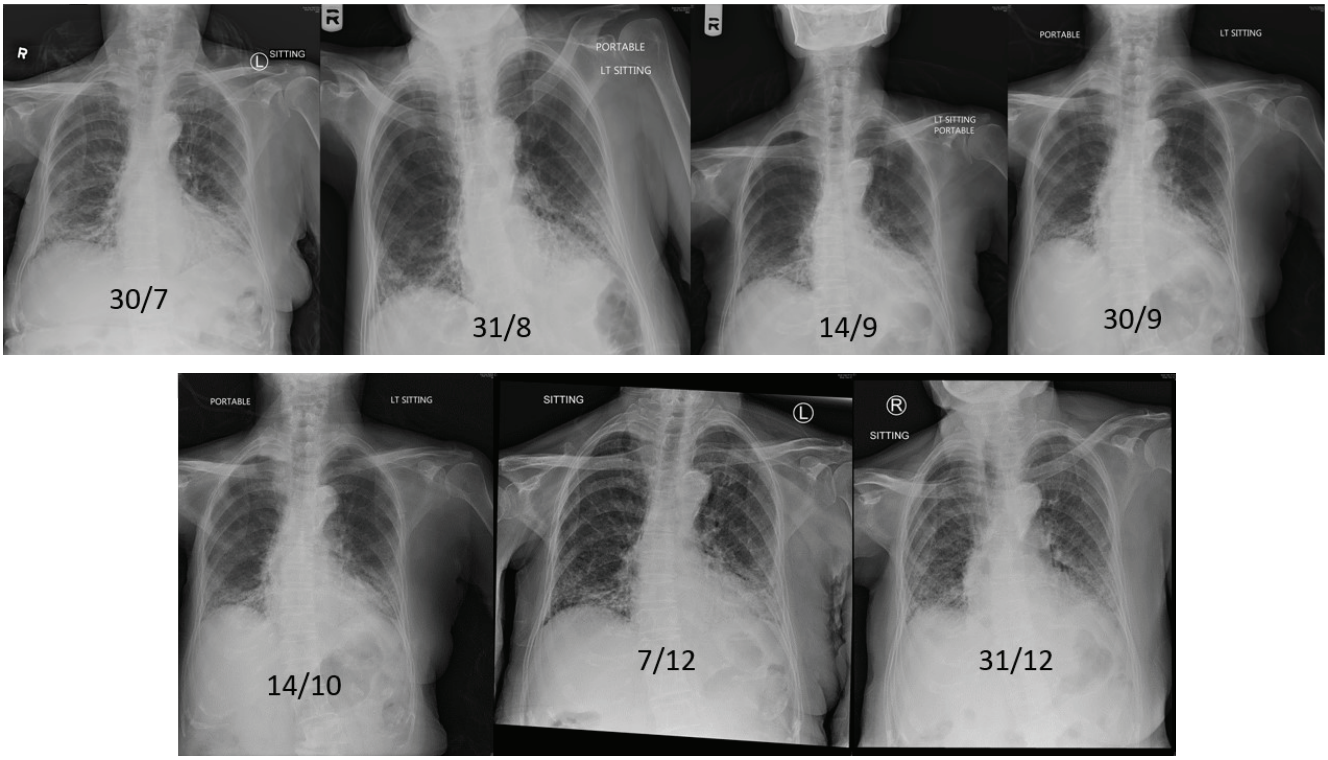




biopsy showed pieces of bronchial mucosa with patchy lymphoplasmacytic infiltrate. Open lung biopsy was offered but the patient declined.

Finally, more blood tests returned and showed elevated ANA (>640), anti-CCP (54 units), positive anti-SSA, anti-SSB and Rheumatoid factor. A diagnosis of primary SjS related ILD was made by the rheumatology team. A tapering dose of prednisolone 40mg daily (0.8mg/kg/day) was started in August 2019. Albeit subjective improvement in dyspnea after training in our rehabilitation ward, the patient had desaturation on exertion and then at rest, and required long term oxygen therapy. Repeated CXR showed static lower zone reticular opacities **(Figure 4)**.

Figure 4. Progress of CXRs in 2019



Nonetheless, on further review of the literature, instead of being a primary disorder, an association of AIs induced SjS was noticed and discussed in the grand round. Opinion from oncology was sought afterwards on the management.

Discussion

We presented the case of a patient with SjS with an insidious onset 10 years after the use of Letrazole. There was first non-specific elevation of ESR and globulin, followed by dry eyes, choking and arthralgia. The diagnosis was made 20 years after the initiation of Letrazole based on clinical and immunological findings. By that time, the patient had already developed ILD. In retrospective, the choking episode and complaints may be a manifestation of dry mouth with salivation and mastication problem. The persistent sinus tachycardia may be a harbinger of pulmonary problem since her thyroid function, as well as Echocardiogram (Ejection fraction 65%) in 2019 were normal, and an earlier holter in 2011 did not reveal any arrhythmia.

Although the patient had a history of radiotherapy, the time course, HRCT appearance, overall clinical picture and presence of immune markers made the diagnosis of radiation induced lung fibrosis unlikely. In addition, there have been no case reports on ILD induced by Letrozole per se[10].

Breast cancer is the most common malignancy diagnosed worldwide in women; more than two million cases are diagnosed every year[11], and it has become the most common cancer affecting women in Hong Kong since 1994[1].

Tamoxifen has been in use for more than 20 years as adjunctive therapy in breast cancer, both in pre and post-menopausal women. Aromatase inhibitors (AI) (Anastrozole, Letrozole and Exemestane) are superior to Tamoxifen in reducing risk of recurrent cancer and has fewer side effects[12-13]. They work by blocking the conversion of androgen from adrenal gland to estrogens, leading to absolute depletion of estrogen in postmenopausal women[12-13].

While arthralgia (46% of patients) and myalgia (15%) are commonly known side effects, as well as osteoporosis, bone fractures and adverse effects on lipid profile and cardiovascular system, more recently, there are case reports on high frequency of development of autoimmune diseases after AIs. Associations that have been reported include Rheumatoid arthritis (RA), SjS, Hashimoto thyroiditis, subacute cutaneous lupus erythematosis, undifferentiated spondyloarthropathy, ankylosing spondylitis, psoriatic arthritis, systemic sclerosis, Systemic lupus erythemastosis, Behcet's disease, primary phospholipid syndrome and Antisynthetase antibody Disease[2-9]. A pathogenic linkage between AI and autoimmune disease is thus hypothesized.

Among various autoimmune diseases, SjS is the second most common one, and is characterized by inflammatory lymphocytic infiltrate of exocrine glands. Patients commonly present with sicca symptoms, fatigue, musculoskeletal pain, as well as multiple systems manifestations including, skin, joint, blood, lung, kidney, etc. It mostly affects middle-aged women, with female to male ratio 9-13 to 1[14].

On the specific association of AIs with SjS **(Table 2)**, Laroche el al first reported in 2007 that among 24 breast cancer patients presented with pain greater than 5/10 on a Visual Analog Scale, 10 were classified to have sicca syndrome. Out of those 10 patients, 9 had positive histological confirmation on salivary gland biopsy and 8 had antinuclear antibodies (ANA). According to the 1986 San Diego criteria, 7 had probable SjS and 1 had definite SjS. It was interesting to note that among those eight patients with positive ANA, only one had inflammatory type of arthritis and hyper- gammaglobulinaemia, whereas our patient had arthralgia only and raised globulin[2]. Around 10 years later, 17 of those 24 patients were followed up after cessation of AI. Most (12/17) had resolution or decrease in joint pain; the RF decreased or became negative, but ANA level fluctuated. Three patients were also noted to have persistent sicca syndrome but there was no information on SjS outcome[15].

In a more recent 2013 case-series, according to the 2002 European criteria, 3 breast cancer women during the first year of adjuvant therapy (Anastrazole in 2 patients and Letrozole in 1 patient) developed SjS. All of them had positive autoimmune antibodies and histopathological confirmation on labial salivary gland biopsies. The author argued that these findings confirm the protective role of estrogens against apoptosis of exocrine secretary glands, as previously suggested[3].

In 2014, there was another case report of a patient

who developed SjS with neuropathy of both legs, after Anastrazole therapy for breast cancer. The exact duration of Anastrazole therapy was not specified but was inferred to be around 6 years from the article. The patient had sicca symptoms for 3 years, followed by lower limb sensory loss for one year before the diagnosis of SjS was made. She required intravenous immunoglobulin for treatment. It was not mentioned in the report whether Anastrazole was stopped. The authors, after excluding other possible causes of neuropathy, such as side effects of chemotherapy, paraneoplastic manifestation or cryoglobulinaemia, concluded that there was a causal relationship between AIs and SjS[4].

Table 2. Summary of literature data about Sjögren Syndrome associated with AIs therapy

Authors	No. of pts	Age (yrs)	Type and duration of AIs therapy	Time from AIs therapy and symptoms	Time from AIs therapy and diagnosis	Diagnosis	Autoimmune laboratory findings
Laroche M 2007 [2]	24	59 (mean age)	Anastrazole (20 pts) Letrozole (4 pts); Duration not reported	2.5 months (mean time)	Not reported	Probable SjS (7 pts), Definite SjS (1 pt), RA (1 pt) Hashimoto thyroiditis (1 pt) Shoulder tendinitis (1 pt) Paraneoplastic aponeurositis (1 pt) OA (2 pts), HCV (2 pts) Unknown (7 pts)	ANA >1/160 (9 pts) RF + (4 pts) anti-CCP (2 pts)
Guidelli GM 2012 [3]	3	60-75	Anastrazole (2 years) (1 pt); Anastrozole (3 years) (1 pt); Letrozole (3 years) (1 pt)	3 months (2 pts); 5 months (1 pt)	1 year (3 pts)	Sjogren Syndrome	RF + (2 pts); ANA + 1/320 (2 pts) anti-Ro-SSA + (2 pts) anti-CCP - (3 pts)
Yasar Bilge NS 2014 [4]	1	70	Anastrazole Duration not reported	Not reported	3 years	Sjogren Syndrome and polyneuropathy	RF +; ANA +; anti-SSA - Anti-SSB -

Our case report was the first one to report the development of SjS with ILD, 20 years after Letrozole. Although no causality could be proven, it would be highly atypical for our patient to develop SjS at the age of 68, since SjS mostly affects middle-age women. Primary Sjögren's syndrome is thought to be due to a complex interaction of genetic, environmental, and hormonal factors. The blockade of estrogens, the key enzyme for the conversion of androgens to estrogens, might have triggered the autoimmune process, and the prolonged duration of AI use might have led to a full-blown manifestation of SjS in the lungs.

While the pathological mechanism behind the possible association of AI and autoimmune disease is yet to be fully elucidated, there is postulation that it is related to the level of estrogens. However, the link is highly complicated. In general, it is believed that at high doses, estrogens suppress Th-1 mediated immune responses and stimulate Th-2 mediated responses. Therefore, in RA, a disease that is Th1 mediated, estrogens deficiency will be a trigger, whereas in SLE, a disease that is Th2 mediated, estrogens will be an exacerbating factor[2, 16].

Indeed, in a cohort of 128 BC patients published in 2019, nearly one third (n: 41; 32%) developed an inflammatory rheumatic disease after the diagnosis of BC. RA was the most frequent diagnosis, followed by SjS, which tallied with the epidemiology of SjS, being the second most common multisystem autoimmune disease[6].

The role of estrogen in SjS in human observational reports, however, had been controversial till 2000's[2]. More insight has recently been gained with the availability of animal model to establish the link of estrogen deficiency and development of SjS. Female aromatase gene knock out mice has been used a model of estrogen deficiency and it has been demonstrated that they spontaneously develop severe autoimmune exocrinopathy resembling SjS, associated with renal involvement, supporting such hypothesis[17]. Furthermore, a significant amount of adiposity in their

salivary glands, with increased number of macrophages and consequent cytokine production were found. Finally, it could be shown that AI administration led to exacerbations of their autoimmune lesions[18].

Back to our patient, given the possibility of AI triggered SjS, with a severe complication of ILD, against a 20-year breast cancer remission period, weighing the risk and benefit, there was a discussion to withhold Letrazole. However, in September 2019, cancer recurrence was found at her axillary lymph node. She was given Exemestane, another AI, by the oncologist since the patient could not afford Fulvestrant injection.

Conclusion

We reported a case of an elderly woman with breast cancer who had Letrozole triggered SjS with ILD. With the increasing incidence of breast cancer and AIs use, physicians and oncologists should be well aware of AIs complications, not just arthralgia but also a whole spectrum of inflammatory arthritis (most commonly RA) and autoimmune disorders, especially in patients who need to stay unusually long on the drug for more than 5-10 years. SjS albeit being the second most common rheumatological disease is particularly difficult to diagnose. Physicians should be more alert to its possibility in breast cancer patients with AI use who have vague complaints of joint pain, dry eyes and dry mouth.

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