Multi-Organ Dysfunction: A Case Report of Indium Poisoning

Shao-Ling Yang1, Yu-Wen Li2, Ming Chen1, Lu Xu1, Nan Li1, Yan-Ru Wang1, Sharvan RAMPERSAD1, Hong Li1, Shen Qu1

1Department of Endocrinology, Shanghai Tenth People’s Hospital, Tongji University School of Medicine, Shanghai, 200072, China
2Department of Endocrinology, Yunnan Third People's Hospital, Yunnan, 650011, China

INTRODUCTION

Indium is a metallic element which belongs to Group III A. The production of indium compounds has increased in manufacture of liquid-crystal panels since the 1990s. Thus indium-processing workers are more exposed to indium compounds. However, public reports of indium poisoning amount only to thirteen cases till now, which were mainly presented as pulmonary damage. We describe a case of a 34-year-old male diagnosed with indium poisoning. Nearly 5 years in the indium powder production and packaging work, Blood, serum and urine indium levels of the patient were found to be very high, 28.8ug/L (NR:<3ug/L), 5.5ug/L (NR:<3ug/L) and 166ug/L (NR:<0.1ug/L) respectively. The result of lung biopsy supported the diagnosis of indium poisoning. This is the first case that manifested as multi-organ dysfunction, involving the pulmonary, haematology, liver, heart, kidneys, pituitary function and glucose metabolism, different from cases before. From this case, it can be seen that the indium has profound impact on multiple body organs.

Keywords: Indium exposure, pulmonary damage, Multi-organ dysfunction

CASE REPORT

History

Patient male, 34 years old, due to “activities after chest tightness, shortness of breath with more than 20 days of systemic edema” admitted. 20 days before admission, patient with chest tightness and shortness of breath, with cough, no phlegm, no chest pain. Self-service of cold medicine, symptoms without remission, systemic anasarca and nocturnal dyspnea progressively appeared, weight gained more than 10kg. Nearly 5 years in the indium powder production and packaging work, for 7-8 hours a day, 4-5 days a week. And his aunt and uncle were suffering from type 2 diabetes. He had no other medical history and was on no medication.

Admission physical examination

T 37.5 ℃, P 124 beats / min, R 27 beats / min, BP 125 / 80mmHg, SpO2 60%, conscious, in an orthopnea position with anemic appearance and clubbed fingers. Obvious anasarca especially in eyelid, scrotum and lower limbs. Little fine basal crackles could be heard in bilateral lungs, not associated with wheezing. Cardiac examinations were normal. In addition, he had obvious abdominal distension and shifting dullness.
Laboratory findings

The anemia related indicators were dropped with Hemoglobin being 76g/L (Normal reference value(NR):130～175g/L ), RBC being 2.96*10^12/L (NR:4.3～5.8*10^12/L), MCH being 25.7pg (NR:27～34pg), MCHC being 310g/L(NR:316～354g/L) while MCV was 82.8fl (NR:82～100fl). Blood routine examination showed that the levels of WBC, NEUT% and PLT were within normal range while the levels of CRP(59.4mg/L) and ESR(70mm/h) were higher than the normal range. Biochemical analysis of serum showed that the liver function may be impaired with albumin being 28g/L (NR:40～55g/L), ALP being 240.4U/L (NR:35～135U/L), γ-GT being 125.2U/L (NR:10～60U/L), while ALT being 2.6U/L (NR:9～50U/L), AST being 10.1U/L (NR:15～40U/L). Kidney function was within normal range with urea nitrogen being 8.0mmol/L (NR:2.76～8.07mmol/L), creatinine being 67.2umol / L (NR:50～104umol/L) and uric acid being 591.4umol/L (NR:208～428umol/L), while the 24h urinary protein was 0.5g(NR:0.028～0.141g). Serum potassium was 5.85mmol/L (NR:3.5～5.3mmol/L), and serum sodium was 136mmol/L (NR:137～147mmol/L). The level of pro-BNP was 5105pg / ml (NR:0～94.6pg/ml). The glucose metabolism related indicator, HbA1c raised to 10.8% (NR:4.5～6.3%), postprandial blood glucose was about 8～10mmol/L, while the levels of FPG(6.3mmol/L) and fasting C-peptide(1.80ng/L) were almost normal. The ACTH level(86.96pg/ml ) was higher than the normal range(NR:7～64pg/ml ), as well as the PRL(386.9mIU/L). Serum testosterone level was decreased (0.1nmol/L), meanwhile, LH and FSH levels both decreased to <0.1mU/L and 0.11mU/L respectively. Thyroid hormones were within normal range except a suppressed TSH level of 0.015mU/L (NR:0.35～5.5mU/L). Transferrin decreased to 0.12nmol/L, while serum iron being 2.0umol/L (NR:10.6～28.3umol/L). Ascitic fluid examination revealed that it was transudate. The indium levels in his blood, serum and urine were 28.8ug/L (NR:<3ug/L), 5.5ug / L (NR:<0.1ug/L) and 166ug/L (NR:<0.1ug/L) respectively.

Auxiliary examination

Ultrasound examination of superficial lymph nodes showed that those lymph nodes, including bilateral cervical lymph nodes, supraclavicular fossa lymph nodes, axillary lymph nodes and inguinal lymph nodes, were all swollen(<2cm). The biopsy of the swollen lymph node indicated reactive hyperplasia. The echocardiography showed a slightly enlarged atrial (inner diameter 47mm) and a little pericardial effusion while the LVFE is 60%. The chest CT (as shown in fig.1) showed diffuse bleeding and edema with inflammatory changes in both lungs, enlarged lymph nodes in mediastinum, hilum and axillary region, a small amount of bilateral pleural effusion, pulmonary hypertension and a small amount of pericardial effusion. The abdominal CT indicated sign of ascites,
lymph nodes in intra-abdominal and retroperitoneal area of multiple sizes and subcutaneous edema. The brain CT and pituitary MR were normal. Bone marrow aspiration showed an iron utilization disorder anemia consistent with the results of blood routine examination and iron metabolism detection. The lung biopsy got a positive result of indium.

**Treatment**

As per the results obtained, the patient was diagnosed with indium poisoning. Initially, diuretic, heart failure treatment, albumin supplements, liver protection, anti-inflammatory treatment was started. However, no significant improvement in edema was noted. After ten-day treatment, ascitic and pleural tapping adding to about 10000mL, the patient was still unwell, no weight loss. Review chest CT (as shown in fig.2), compared with chest CT on admission showed new changes, including diffuse exudative lesion, interstitial pneumonia and little pleural effusion in both lungs.

**DISCUSSION**

Along with cases about occupational hazards caused by indium exposure were published, several epidemiological surveys had been undertaken in Japan. In 2002, Chonan had performed a pulmonary examination on male workers in an indium processing industry [5]. The result indicated that workers with high level of indium in serum had greater interstitial change on high resolution CT (HRCT). Hereafter, Hamachi and Nakano had performed cross-sectional surveys respectively [6-8]. According to the studies above, there existed sharp dose-effect relationship between indium exposure and the degree of pulmonary change. Exposure to indium compounds represented a risk of pulmonary damage [9]. A prolonged risk of pulmonary and systemic diseases still remains even after withdrawal from exposure [10].

In some animal experiments, studies found that indium can be absorbed into the blood and quickly transported to the soft tissue and bone, mostly in the liver, kidney, lung, spleen, testes. The biological half-life of indium in serum was estimated to be 8.09 years [3]. It was indicated that fecal excretion served as the major route for indium elimination [1]. As for the toxicity of indium compounds, it had been reported to exhibit pulmonary toxicity in animal experiments [11]. Also, indium compounds have chronic damage on animal kidney, liver, growth and development, reproductive system [12-14]. In rats observed a certain carcinogenic effect [15].

The mechanism how indium causes pulmonary damage remains unknown. Some hypothesis thought
that the indium compounds absorbed into the body may induce an inflammatory response, with the macrophage dysfunction, alveolar accumulation of lipoprotein, and eventually resulting in pulmonary fibrosis and emphysema [8, 16]. In Noguchi’s study, they also put forward the idea that pulmonary alveolar proteinases occurs as an acute phase response and is replaced by fibrosis after long term latency [17]. To better understand the association, more research needs to be established to elucidate the mechanism of indium poisoning.

Currently, there were few case reports related with indium poisoning, and all of them were focused on its pulmonary manifestations. Similarly, previous epidemiological studies also demonstrated pulmonary changes. However, that is not the only manifestation in our case, the difference is that the present case report is the first to describe the multi-organ damage caused by indium poisoning comprehensively. The damage done in this case was not confined to the lungs, multiple organs were also involved. They are listed as follows.

Firstly, for the hematolgy, the blood routine test prompted a microcytic anemia (Hb 76g/ L). The bone marrow aspiration showed an iron utilization disorder anemia consistent with the blood routine and iron metabolism results. Therefore, the impact of indium on the hematolgy could manifest as a microcytic, iron utilization disorder anemia.

Secondly, for the liver, the level of albumin was apparently decreased(24-28g/L) while the liver enzymes were almost normal, which remind us that the toxicity of indium to the liver mainly resulted in dysfunction of liver synthesis, no hepatocyte destruction and no elevated liver enzymes.

Thirdly, for the heart, the main manifestation of the patient included dyspnea on exertion, paroxysmal nocturnal dyspnea and apparent anasarca. The BNP was significantly elevated to 5105pg / ml. Also the echocardiography showed a slightly enlarged atrial. All above suggested a myocardial injury induced by indium.

Next, for the kidneys, about a week or so after admission, the patient had hyperkalemia due to improper diet. Serum potassium level fluctuated between 5.5-5.9mmol/L, with a urine output of about 700-900ml/24h under the use of diuretics. Even the use of cortisol could not effectively reduce the potassium level. Combined with the fact that the level of indium in urine is about 166-117ug/L (normal <0.1ug/L), it is obvious that the kidney is an important channel of indium excretion which lead to damage to the kidney, especially the renal tubules, rather than the glomerulus.

Additionally, for pituitary function, it showed low level of several pituitary related hormones such as TSH, LH, FSH. The level of ACTH increased slightly initially, maybe due to the stressful situation, and then declined. All above indicated the impaired function of the hypothalamus-pituitary-thyroid axis, hypothalamus-pituitary-gonadal axis and hypothalamus-pituitary-adrenal axis which was the consequence of indium poisoning on those endocrine glands and reminded us that indium was an important endocrine disruptors.

Besides, for the glucose metabolism, the level of HbA1c raised to 10.8%, postprandial blood glucose was about 8 ~ 10mmol/L, and the levels of FPG(6.3mmol/L) were almost normal at first and then increased significantly (> 30mmol/L) following use of glucocorticoids. The HbA1c does not match with blood glucose that we cannot exclude the influence which indium made on glycated hemoglobin directly, and the anemia condition may affect the detection indicators. In terms of type of diabetes in the patient, it is unclear to classified as type 2 diabetes or special type of diabetes, incorporating that there was a family history of diabetes and hit by indium poisoning.

Moreover, for the edema and multiple serous cavities effusion, the hypoalbuminemia, heart failure and the change in vascular permeability may be the direct major factors for edema, but it was still difficult to relieve the edema even after active support with protein and even under a cardiac EF at 60%. The level of indium in ascites increased. From above we could see that the indium had a direct impact on blood vessels and serous cavity.

Finally, for lymph nodes, multiple enlarged lymph nodes and the reactive hyperplasia change may be the joint effects of many factors such as indium poisoning, inflammation and effusion. In our patient, after excluding diseases like the POEMS syndrome, connective tissue diseases and tuberculosis, the diagnosis of indium poisoning is clear. In order to furtherly identify the exposure of indium in this patient, we chose two colleagues of the patient in the same worksite, one is an office staff and the other is working for indium processing in recent 3 years, and had their blood tested. We found that the indium level in serum of the indium processing worker is much higher than the office staff. The result further supported the diagnosis of the patient.

So far the main measure is symptomatic and supportive treatment, for there is no specific antidote for indium poisoning. Broncho alveolar lavage may be done if necessary. In this case, the application of methylprednisolone was obviously effective in the case. Whether the methylprednisolone reduced the inflammation, increased the vascular tone and improved the capillary permeability, thereby reducing transudate and edema, or it just inhibited the immune responses indirectly getting multi-organ protection was unclear. Do the patients of indium poisoning be appropriate of the impact of corticosteroids at early time? Further
studies are needed to prove the above. The key lies in early prevention. The Japan Society for Occupational Health (JSOH) suggested that we should have physical examination on occupational indium exposures about 1-

2 times annually. Based on the epidemiological studies, JSOH proposed 3 ug/l of indium in serum as an occupational exposure limit.

Fig-4: The chest CT of patient in six months after discharge

After 6 month, the review of some indicators of the patient showed that the level of hemoglobin, albumin, and pituitary related hormones (except ACTH being 84.22pg/ml) almost returned to normal, which indicated that the function of several aforementioned organs was significantly restored. However, the HbA1c was 7.1% with a secretion peak detention in insulin secretion curve. The level of γ-GT rose to 236.6U/L. The chest CT (as shown in fig.4) still indicated interstitial change. The bone mineral density examination revealed osteoporosis (T score: L1-L4 -2.0, right hip -1.5, and femoral neck -2.0). Moreover, the level of indium in blood and urine were still above normal (25.8ug/L; 7.52ug/L) which indicates that long-term follow-up was necessary to evaluate the long term effects.

CONCLUSION

In summary, this paper firstly not only described the manifestations and treatment of multi-organ dysfunction caused by indium poisoning in detail, but also provided the most integrated case data. The indium poisoning can cause systemic multi-organ dysfunction, not limited to the lungs. For indium-exposed workers, attentions should not only be paid to the lungs, but also the screening on function of other organs. And long-term follow-up of indium-exposed workers is essential to clarify the natural history of indium poisoning. Meanwhile we called to the related department to establish clinical diagnostic criteria and propose the treatment of occupational indium poisoning as soon as possible.

Abbreviations


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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

REFERENCES