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Adult-Onset Still's Disease Presenting as FDG-Avid Lymphadenopathy Mimicking Lymphoma: A Diagnostic Pitfall in Pyrexia of Unknown Origin

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ABSTRACT

Adult-onset Still's disease is an uncommon systemic autoinflammatory condition that can present with non-specific clinical features and pose a significant diagnostic challenge. We report the case of a woman in her late 50s presenting with prolonged pyrexia of unknown origin, systemic inflammation, polyarthralgia, and an evanescent rash. Laboratory investigations revealed marked hyperferritinaemia (>2000~µg/L), elevated inflammatory markers (C-reactive protein peaking at 266~mg/L), and neutrophilic leukocytosis. Extensive infectious and autoimmune investigations were negative. Positron emission tomography-computed tomography demonstrated widespread fluorodeoxyglucose-avid lymphadenopathy and splenic uptake, raising strong suspicion for lymphoma. However, subsequent ultrasound imaging revealed preserved nodal architecture, and biopsy was deferred. Following multidisciplinary evaluation, a diagnosis of late-onset adult-onset Still's disease was established using Yamaguchi criteria. The patient responded rapidly to corticosteroid therapy, with complete clinical and biochemical remission. This case highlights the diagnostic complexity of adult-onset Still's disease, particularly when presenting with PET-avid lymphadenopathy, and underscores the importance of integrating clinical, biochemical, and imaging findings to avoid misdiagnosis and unnecessary invasive procedures.

Keywords: *Adult-Onset Still's Disease, Pyrexia of Unknown Origin, Hyperferritinaemia, FDG-PET, Diagnostic Dilemma, Yamaguchi Criteria, Lymphadenopathy*

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder characterised by quotidian high-spiking fevers, an evanescent rash, arthralgia, and systemic inflammation (Gerfaud-Valentin *et al*., 2014; Fautrel, 2008). It represents an important but often under-recognised cause of pyrexia of unknown origin (PUO), frequently leading to extensive diagnostic evaluation and delayed diagnosis.

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The estimated incidence of AOSD is approximately 0.16 cases per 100,000 individuals per year, contributing to limited clinical familiarity and diagnostic uncertainty (Fautrel, 2008). The underlying pathophysiology involves dysregulated activation of the innate immune system, with key roles for pro-inflammatory cytokines including interleukin-1, interleukin-6, and interleukin-18 (Feist *et al*., 2018; Giacomelli *et al*., 2018). As such, AOSD is increasingly recognised within the spectrum of autoinflammatory disorders rather than classical autoimmune disease (Giacomelli *et al*., 2018).

AOSD remains a diagnosis of exclusion, necessitating comprehensive investigation to rule out infectious, malignant, and alternative autoimmune conditions (Fautrel, 2008; Gopalarathinam *et al*., 2016). This often results in prolonged diagnostic pathways, particularly in patients presenting with PUO. Laboratory findings typically demonstrate markedly elevated inflammatory markers, including neutrophilic leukocytosis and hyperferritinaemia, reflecting systemic inflammation and macrophage activation (Gerfaud-Valentin *et al*., 2014; Mehta and Efthimiou, 2012). Although hyperferritinaemia is a characteristic feature, it remains non-specific and may also be observed in infection, malignancy, and hyperinflammatory syndromes such as haemophagocytic lymphohistiocytosis (HLH) (Mehta and Efthimiou, 2012; Yamashita *et al*., 2014).

A key diagnostic challenge lies in the clinical and radiological overlap between AOSD and haematological malignancies, particularly lymphoma. Shared features include fever, lymphadenopathy, and systemic inflammation, which can complicate early diagnostic assessment (Gerfaud-Valentin *et al*., 2014; Gopalarathinam *et al*., 2016). This challenge is further compounded by imaging findings, as fluorodeoxyglucose positron emission tomography (FDG-PET) may demonstrate intense metabolic activity in lymph nodes and the spleen secondary to cytokine-driven inflammation, closely mimicking lymphoproliferative disease (Yamashita *et al*., 2014; Carter *et al*., 2019).

Furthermore, hyperinflammatory syndromes such as HLH must be carefully considered in the differential diagnosis due to overlapping clinical and biochemical features, including fever, cytopenias, and elevated ferritin levels, although these conditions differ significantly in clinical trajectory and management (Yamashita *et al*., 2014; Kaçar and Celkan, 2022).

We present a case of late-onset AOSD presenting with prolonged PUO and widespread FDG-avid lymphadenopathy highly suggestive of lymphoma, highlighting an important diagnostic pitfall and the importance of multimodal assessment in achieving an accurate diagnosis.

Case Presentation

A woman in her late 50s with a history of intervertebral disc prolapse presented with a two-day history of lethargy, myalgia, sore throat, rigors, and coryzal symptoms. She also reported a severe self-resolving headache and difficulty mobilising due to profound fatigue.

On examination, she was alert and haemodynamically stable but hypotensive (91/62~mmHg) and initially afebrile. A blanching macular erythematous rash was noted over the abdomen, back, and buttocks.

During admission, she developed recurrent spiking fevers up to 40^{\circ}C with a quotidian pattern. These episodes were associated with polyarthralgia affecting the wrists, knees, and ankles, a transient salmon-pink rash coinciding with fever spikes, rigors, and profound fatigue. Between febrile episodes, she experienced relative symptomatic improvement, a pattern consistent with autoinflammatory disease (Gopalarathinam *et al*., 2016).

Initial laboratory investigations demonstrated a marked inflammatory response (Table 1), including significantly elevated CRP, neutrophilic leukocytosis, and hyperferritinaemia (>2000~µg/L), findings characteristic of AOSD (Gerfaud-Valentin *et al*., 2014).

Table 1: Initial Laboratory Findings.

Parameter	Value	Reference Range	Units	Interpretation
CRP	161 (peak 266)	<5	~mg/L	Markedly elevated
WCC	11.4	4.0–11.0	\times 10^{9}/L	Mild leukocytosis
Neutrophils	9.6	1.7–7.5	\times 10^{9}/L	Neutrophilia
Platelets	87 (initial)	150–450	\times 10^{9}/L	Transient thrombocytopenia
ALT	60	<35	UL−1	Mild elevation
ALP	74 (peak 191)	30–130	UL−1	Elevated
Ferritin	>2000	15–150	~\mu g/L	Markedly elevated
ESR	79	<20	~mm/hr	Elevated

Extensive infectious investigations, including blood cultures, cerebrospinal fluid analysis, viral PCR, and serology, were negative. Autoimmune screening was also unremarkable.

Computed tomography (CT) imaging showed no malignancy or significant lymphadenopathy. However, PET-CT demonstrated widespread FDG-avid lymphadenopathy above and below the diaphragm, along with splenic uptake, raising concern for lymphoma (Fig. 1-4) (Yamashita *et al*., 2014).

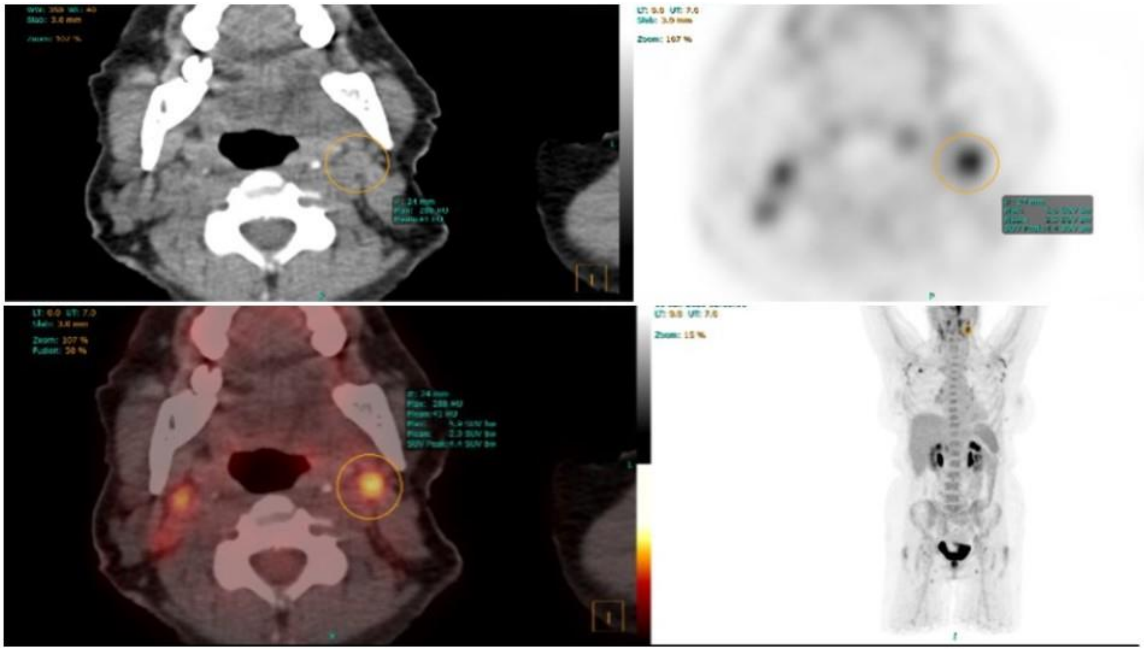

Figure 1: Cervical lymphadenopathy on PET-CT: Fluorodeoxyglucose (FDG) PET-CT demonstrating multiple mildly to moderately FDG-avid cervical lymph nodes. The circled region highlights a representative level II lymph node on the left measuring approximately 11 × 7 mm with a maximum standardized uptake value (SUVmax) of 5.9. The distribution and metabolic activity raised suspicion for lymphoproliferative disease.

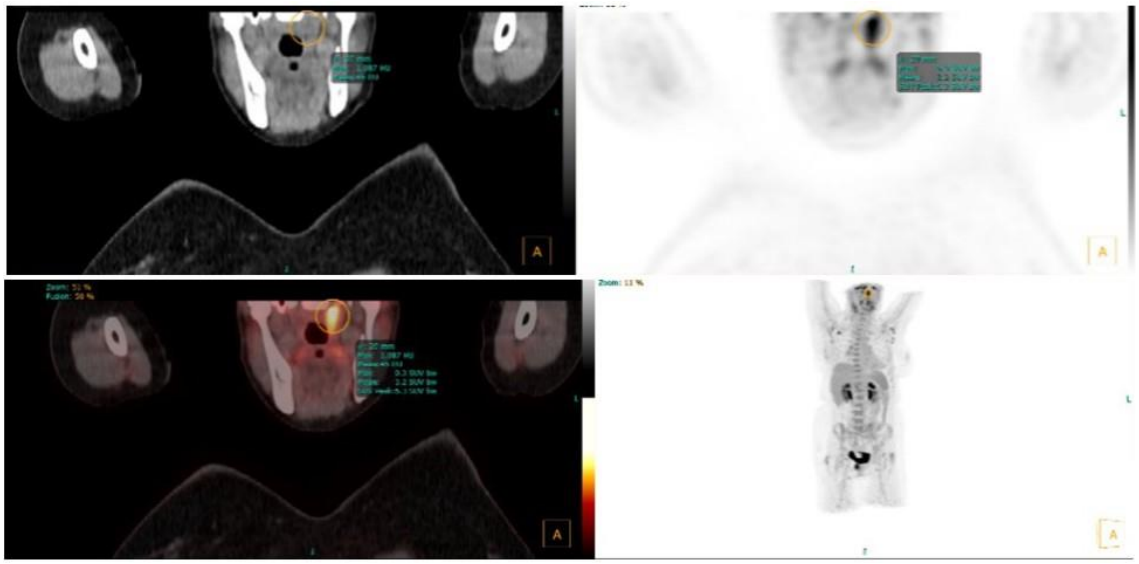

Figure 2: Nasopharyngeal FDG uptake: FDG PET-CT showing asymmetrical uptake in the left nasopharynx, extending towards the fossa of Rosenmüller. The circled area indicates the region of increased metabolic activity, measuring approximately 1.5 × 1 cm with an SUVmax of 9.3. These findings were initially concerning for malignancy and prompted further otolaryngology evaluation.

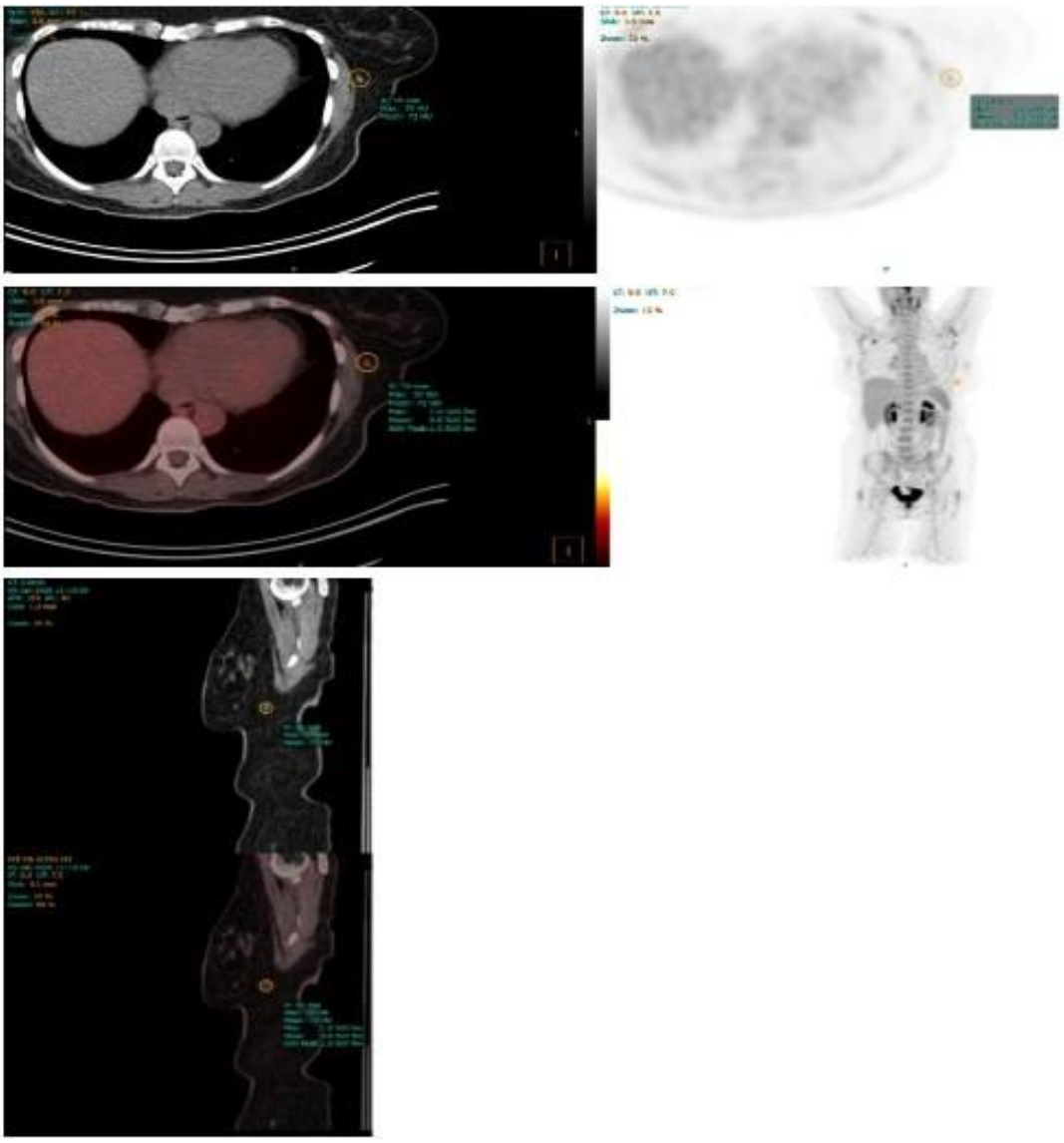

Figure 3: Breast-region nodal uptake: FDG PET-CT demonstrating small, faintly FDG-avid nodules/nodes within or adjacent to the posterior lower regions of both breasts. The circled region highlight the left sided findings, measuring approximately 7 × 5 mm (SUVmax 1.8). On the right side the region measured 6 × 4 mm (SUVmax 1.7). These were considered likely nodal rather than primary breast lesions but contributed to the overall suspicion of systemic disease.

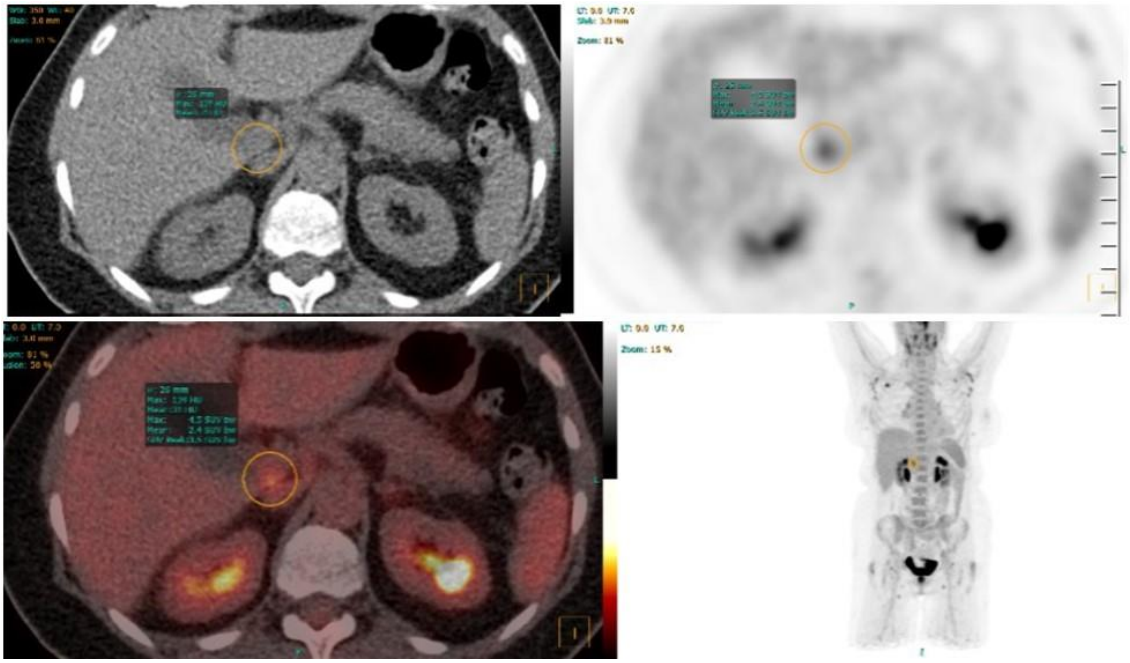

Figure 4: Subdiaphragmatic lymph node uptake: FDG PET-CT demonstrating a mildly FDG-avid lymph node in the porto-caval region beneath the diaphragm. The circled region identifies this node, with an SUVmax of 4.5. This finding formed part of the widespread nodal uptake pattern suggestive of systemic pathology.

Ultrasound of the lymph nodes demonstrated preserved fatty hila and reactive morphology, and biopsy was deferred. ENT evaluation of nasopharyngeal uptake was normal. Musculoskeletal imaging showed no erosive arthropathy.

Differential diagnoses included infection, malignancy, haemophagocytic lymphohistiocytosis (HLH), and AOSD. HLH was considered due to fever, hyperferritinaemia, and cytopenias; however, the patient did not meet diagnostic criteria, lacking persistent cytopenias, hypofibrinogenaemia, and hypertriglyceridaemia (Carter *et al*., 2019; Kaçar and Celkan, 2022).

A diagnosis of AOSD was established based on Yamaguchi criteria (Gopalarathinam *et al*., 2016). The patient was commenced on oral prednisolone (40 mg daily), resulting in rapid clinical improvement and normalisation of inflammatory markers.

Discussion

AOSD remains a diagnostic challenge, particularly in patients presenting with PUO. Its clinical features frequently overlap with infection, malignancy, and other inflammatory conditions, often resulting in delayed diagnosis (Gerfaud-Valentin *et al*., 2014; Gopalarathinam *et al*., 2016).

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A key learning point from this case is the importance of reassessing the diagnosis in patients who fail to respond to appropriate antimicrobial therapy. Persistent fever and rising inflammatory markers despite broad-spectrum antibiotics should prompt consideration of non-infectious causes, including AOSD (Gopalarathinam *et al*., 2016).

Hyperferritinaemia is a characteristic feature of AOSD and may serve as an important diagnostic clue, reflecting macrophage activation and systemic inflammation (Mehta and Efthimiou, 2012). However, ferritin is non-specific and must be interpreted in context.

HLH is an important differential diagnosis, given overlapping features such as fever and elevated ferritin. However, HLH is typically associated with progressive cytopenias and organ dysfunction, which were not observed in this case (Carter *et al*., 2019; Kaçar and Celkan, 2022).

The presence of FDG-avid lymphadenopathy on PET imaging represents a recognised diagnostic pitfall. Inflammatory lymphadenopathy in AOSD can demonstrate significant metabolic activity, closely mimicking lymphoma (Yamashita *et al*., 2014). Careful correlation with ultrasound findings was essential in avoiding unnecessary invasive procedures.

Diagnosis was supported by the Yamaguchi criteria, which remain a practical and sensitive tool for AOSD classification (Gopalarathinam *et al*., 2016). Multidisciplinary input was crucial in reaching a diagnosis.

This case also highlights the psychological burden associated with diagnostic uncertainty, particularly when malignancy is suspected.

Conclusion

This case highlights adult-onset Still's disease as an important differential diagnosis in patients presenting with pyrexia of unknown origin and persistent systemic inflammation. It underscores the diagnostic challenges posed by overlapping clinical and imaging features with infection and malignancy, particularly the potential for FDG-avid lymphadenopathy to mimic lymphoma. Lack of response to antimicrobial therapy should prompt early reconsideration of alternative diagnoses. Early recognition and multidisciplinary assessment are essential to facilitate appropriate treatment and reduce patient burden.

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Ethics Statement: Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest: I, Laura Vahey, declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions: I, Laura Vahey, solely conceived and designed the study, collected and interpreted the clinical data, and drafted and critically revised the manuscript. I approved the final version for submission and agree to be accountable for all aspects of the work.

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