CANINE CONUNDRUM: A TALE OF AN UNEXPECTED TRANSIENT LEUCOCYTOSIS

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Specimen:

EDTA whole blood and blood smear; Serum biochemistry; Fine needle aspirate (FNA) from a cutaneous nodule

History:

A five-year-old female neutered Beagle presented to a first-opinion veterinary centre with complaints of lethargy, vomiting, and decreased appetite. Physical examination revealed no significant abnormalities, except for a mild hyperthermia (39.7°C [37.5-39.3°C]) and a recently noted cutaneous thickness on the right thigh.

Clinical findings:

Biochemistry results showed a marked C-reactive protein (CRP) elevation (201mg/L [0-15mg/L]). Haematological evaluation (Sysmex XN-V analyser) (Table 1) demonstrated moderate genuine thrombocytopenia (62 x 10^9/L [150-500 x 10^9/L]) and marked leucocytosis (46.1 x 10^9/L [6.0-15.0 x 10^9/L]), with abnormal scattergram analysis indicating an abnormal distribution of cells (Figure 1). Blood smear examination revealed a predominance of abnormal cells, accounting for 80% of all nucleated cells (Figure 2). Flow cytometry testing was recommended, but logistical delays in transportation led to the sample deterioration, making it unsuitable for analysis. As a result, a follow-up haematological assessment (Sysmex XN-V analyser) was conducted two weeks later and revealed a shift to mild thrombocytosis (650 x 10^9/L [150-500 x 10^9/L]), while all other parameters were within the reference range, including the white blood cell counting with no microscopic evidence of

circulating atypical cells. This precluded the need for further flow cytometry testing. Simultaneously with the latter sample, cytology from the subcutaneous mass on the right lateral thigh was obtained (Figure 3). It is worth noting that during this period, the patient received only a gastrointestinal diet, with no medications administered.

Questions:

- Considering the initial scattergram and blood smear findings, what differential diagnoses would you propose for the haematological results?
- How would you correlate the cytological findings of the skin nodule with the initial haematological blood results?
- What are the possible explanations for the disappearance of the haematological abnormalities in the second blood sample?

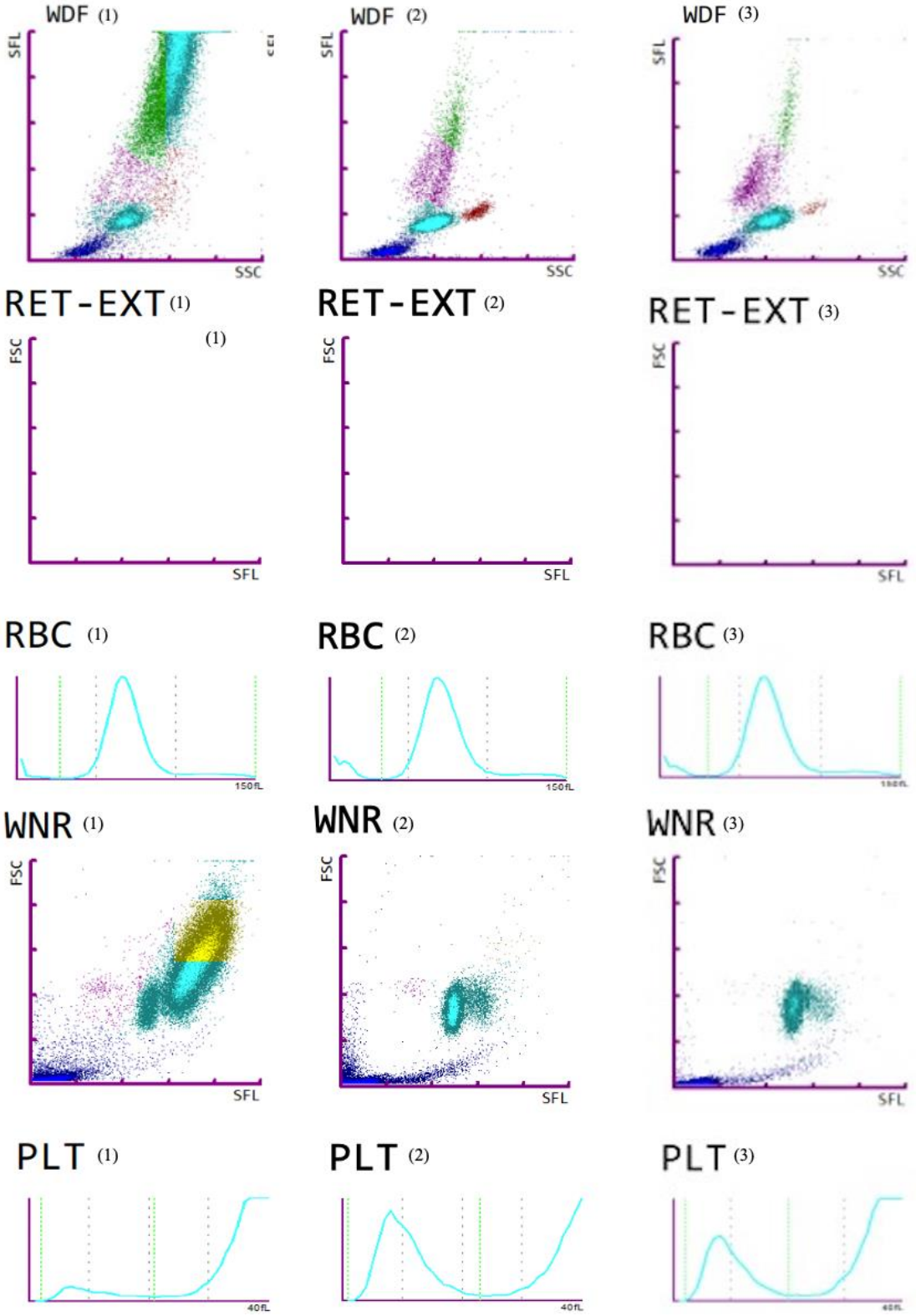

Figure 1: Sysmex XN-V analyser scattergrams of the WBC differential fluorescence (WDF), reticulocyte extended (RET-EXT), red blood cell channel (RBC), white count and nucleated red blood cells channel (WNR), and platelet channel (PLT). (1) Left Scattergram - WDF: Initial haematology result showing an atypical cellular distribution with a prominent population of highly fluorescent cells. The WNR scattergram indicates a large population of WBCs (light blue) and a significant group of cells in the basophil area (yellow). (2) Middle Scattergram - WDF: Subsequent haematology sample taken two weeks later, demonstrating a normal distribution of leucocyte subpopulations. (3) Right Scattergram - WDF: Haematology sample from a canine patient with values within the normal reference range.

Table 1: Presentation of the haematology results obtained using a Sysmex XN-V haematology analyser. Results (1) = First haematology results from 31/10/2023; Results (2) = Second haematology results (two weeks later from 14/11/2023); RI = Reference intervals.

	Results (1)	Results (2)	RI	Units
ERYTHROGRAM				
RBC	6.33	6.81	5.50-8.50	10^{12}/L
HGB	14.7	16.2	12.0-18.0	g/dL
HCT	0.43	0.47	0.37-0.55	ratio
MCV	67.3	69.2	60.0-77.0	fL
MCH	23.1	23.8	19.0-26.0	Pg
MCHC	34.3	34.4	32.0-39.0	g/dL
RDW	13.6	16.7		%
PLATELETS	↓ **62**	↑ **650**	150-500	10^9/L
LEUCOGRAM				
LEUCOCYTES	↑ **46.1**	11.3	6.0-15.0	10^9/L
NEUTROPHILS	↑ **20.95**	8.56	3.00-11.50	10^9/L
% NEUTROPHILS	45.5	75.9		%
LYMPHOCYTES	↓ **0.27**	1.30	1.00-5.00	10^9/L
% LYMPHOCYTES	0.6	11.5		%
MONOCYTES	↑ **4.86**	0.80	0.00-1.40	10^9/L
% MONOCYTES	10.5	7.1		%
EOSINOPHILS	0.33	0.57	0.00-1.25	10^9/L
% EOSINOPHILS	0.7	5.1		%
BASOPHILS	↑ **19.68**	0.05	0.00-.0.20	10^9/L
% BASOPHILS	42.7	0.4		%
NRBC	0.41	0.06		10^9/L
% NRBC	0.9	0.5		%

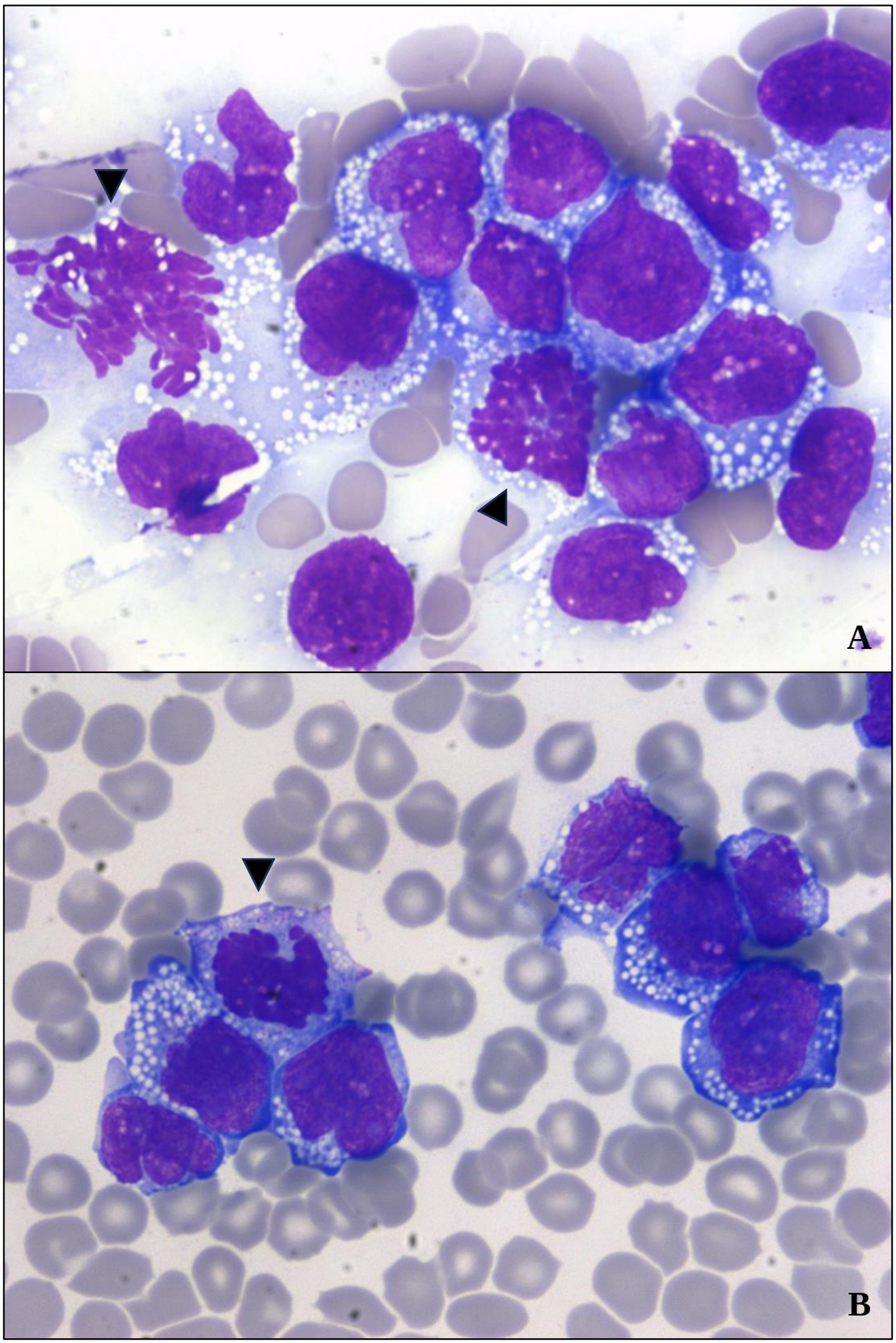

Figure 2: Blood smear from the first haematology blood sampling showing atypical circulating haematopoietic cells. Feathered edge (A) and monolayer (B) of the blood smear. Mitotic figure indicated by arrowhead. Wright-Giemsa, 50x objective.

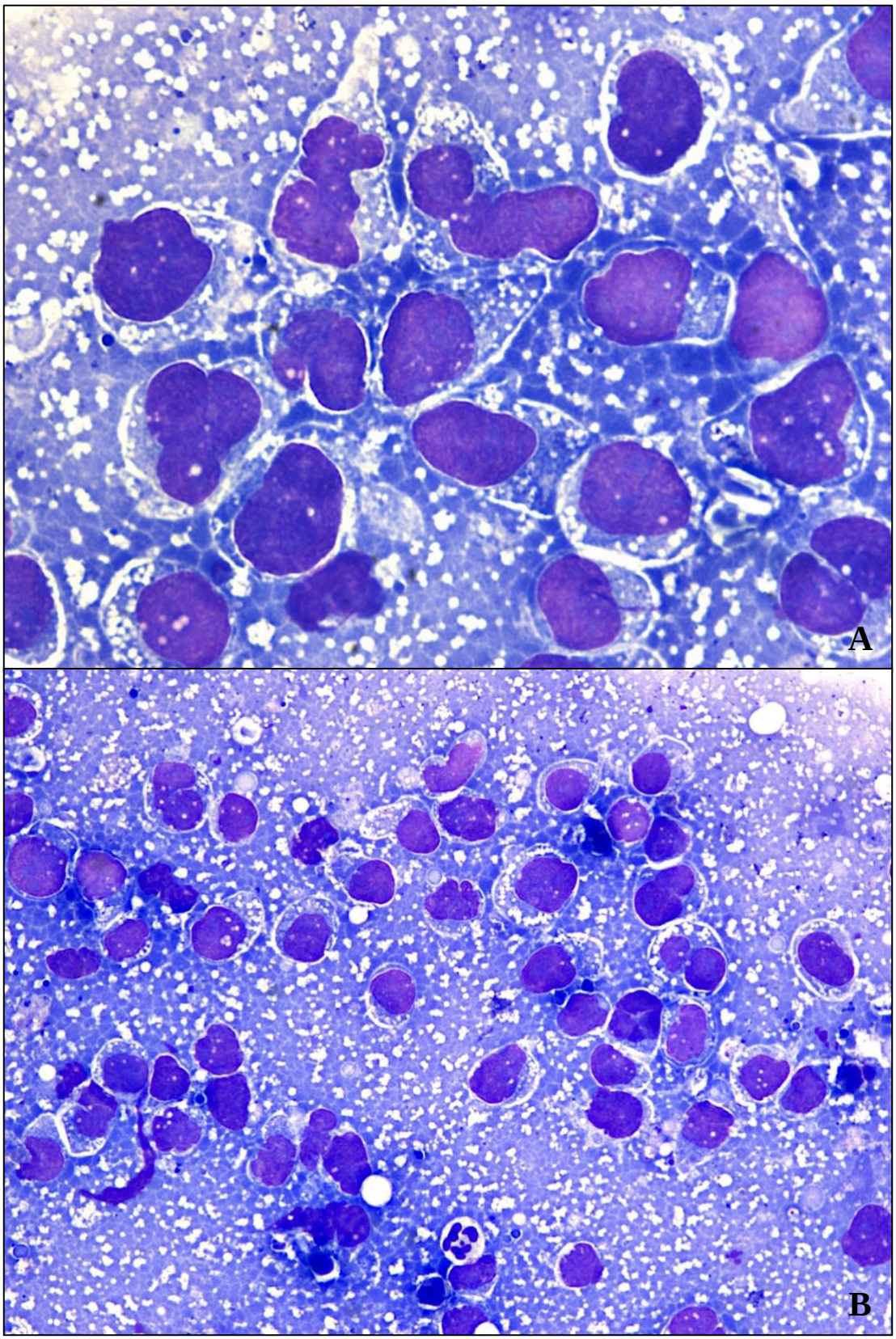

Figure 3: Fine needle aspiration from the right lateral thigh cutaneous nodule showing the predominant cell population present. Wright-Giemsa, 50x and 20x objectives, A and B, respectively.

Interpretation/Diagnosis:

Undetermined cutaneous round cell neoplasia with a transient leukaemia

Additional information:

Peripheral blood (first haematology sample):

- Blood smear: The evaluation revealed an abnormal population of round cells exhibiting distinct characteristics (Figure 2). These included eccentrically positioned round nuclei, often indented to cerebriform, with finely stippled smooth chromatin, and frequent single to multiple prominent nucleoli. These cells displayed moderate amounts of deeply basophilic cytoplasm with frequent small clear vacuoles, occasional a fine pink cytoplasmatic granulation, and evidence of mitotic activity. Rare binucleated cells were noted. Furthermore, manual platelet count confirmed the reported thrombocytopenia, with no observed platelet clumps. Acute leukaemia was initially suspected.

- Immunocytochemistry: Immunocytochemistry from a previous stained blood smear corroborated the presence of neoplastic cells, with over 80% displaying faint cytoplasmic/membrane CD3 staining (Figure 4A) and more than 95% exhibiting positive Ki67 expression (Figure 4B). The marker Pax5 was negative on the neoplastic cells (Figure 5). These results supported the diagnosis of T-cell lymphoma/leukaemia.

- PCR for Antigen Receptor Rearrangements (PARR): A weak monoclonal proliferation of the T lymphocytes was detected. Additionally, T lymphocytes of polyclonal origin were detected (unspecific "background"). The population of B lymphocytes showed a regular polyclonal reaction pattern. These results indicated the presence of a clonal T lymphoid cell population, suggestive of T-cell lymphoma/leukaemia.

Skin nodule(s):

- Cytology: The cytological examination of the skin nodule located on the right lateral thigh displayed a basophilic smooth to mildly granular background with a predominant population of large round cells (Figure 3 and 6). These cells exhibited a small amount of deep basophilic cytoplasm with multiple small clear vacuoles, and single to multiple round to indented, occasionally cerebriform nuclei with finely stippled chromatin and multiple nucleoli. A foamy to tigroid background composed by a mix of clear vacuoles and blue cytoplasmic fragments. The cytological features were consistent with an undetermined round cell neoplasia, mirroring the morphological features observed in the blood smear.

- Flow cytometry description: The flow cytometry was performed on fluid rinse of FNA specimens of the skin nodule located on the right lateral thigh and of an ear mass. Due to the low cellularity, limited markers have been tested (Table 2). The result was CD8+ T cell lymphoma/leukaemia

Table 2: Presentation of the flow cytometry findings on the mass located on the leg and ear. TP = Target population, corresponding to the region of intermediate and large lymphoid/mononuclear cells; NT = Not tested due to scarce cellularity.

MARKERS	LEG MASS	EAR MASS
CD5	Positive in 52% of TP	Positive in 95% of TP
CD21	Positive in 17% of TP	Positive in 13% of TP
CD8	NT	Positive in 46% of TP
CD4	NT	Positive in 16% of TP
Notes	Very low cellularity	Low cellularity

- Histopathology: Histopathological analysis of the skin nodule located on the right lateral thigh demonstrated densely packed round cells of medium to large size displaying moderate nuclear pleomorphism, with a predominance of relatively small nuclei and exceptionally high numbers of mitotic figures (up to 20/hpf) (Figure 7). No convincing evidence of epitheliotropism was observed, but an extension into the underlying fat was detected, supporting the diagnosis of a cutaneous lymphoma.

- Immunohistochemistry: The majority of the neoplastic cells from the skin nodule located on the right lateral thigh were positive for CD3 (Figure 8), although the intensity of the staining was variable and faint in most cells. Immunohistochemical results were consistent with a T-cell lymphoma.

Other exams:

- Radiography: The thoracic study largely fell within normal parameters. There was a mild diffuse interstitial pattern, possible likely artefactual (exposure factors, body condition of the patient) and less likely to unlikely diffuse neoplastic infiltration (e.g., lymphoma); prominent aortic arch due to individual variant, systemic hypertension or other factors and moderately increased body condition.

- Abdominal ultrasound: The abdominal ultrasound predominantly revealed normal findings, with a minor observation of hepatomegaly likely attributed to individual variation, rather than indicating a significant concern such as malignancy.

- Cytology from liver: There was a predominance of well-differentiated hepatocytes exhibiting mild to moderate cytoplasmatic vacuolation and no signs of metastatic infiltration were observed.

- Cytology from spleen: There was evidence of extramedullary haematopoiesis, and no signs of metastatic infiltration were observed.

- Cytology from enlarged lymph nodes: The specimens were obtained from the right and left mandibular lymph nodes and right prescapular lymph node (Figure 9). The background presented some cytoplasmatic fragments. A large round cell population was predominant, with a small amount of basophilic cytoplasm frequently having multiple small clear vacuoles, round to indented nuclei with finely stippled chromatin, and single to multiple nucleoli. Some small lymphocytes, a few plasma cells, and neutrophils were also seen. These cytological features were consistent with a presumptive lymphoid neoplasia.

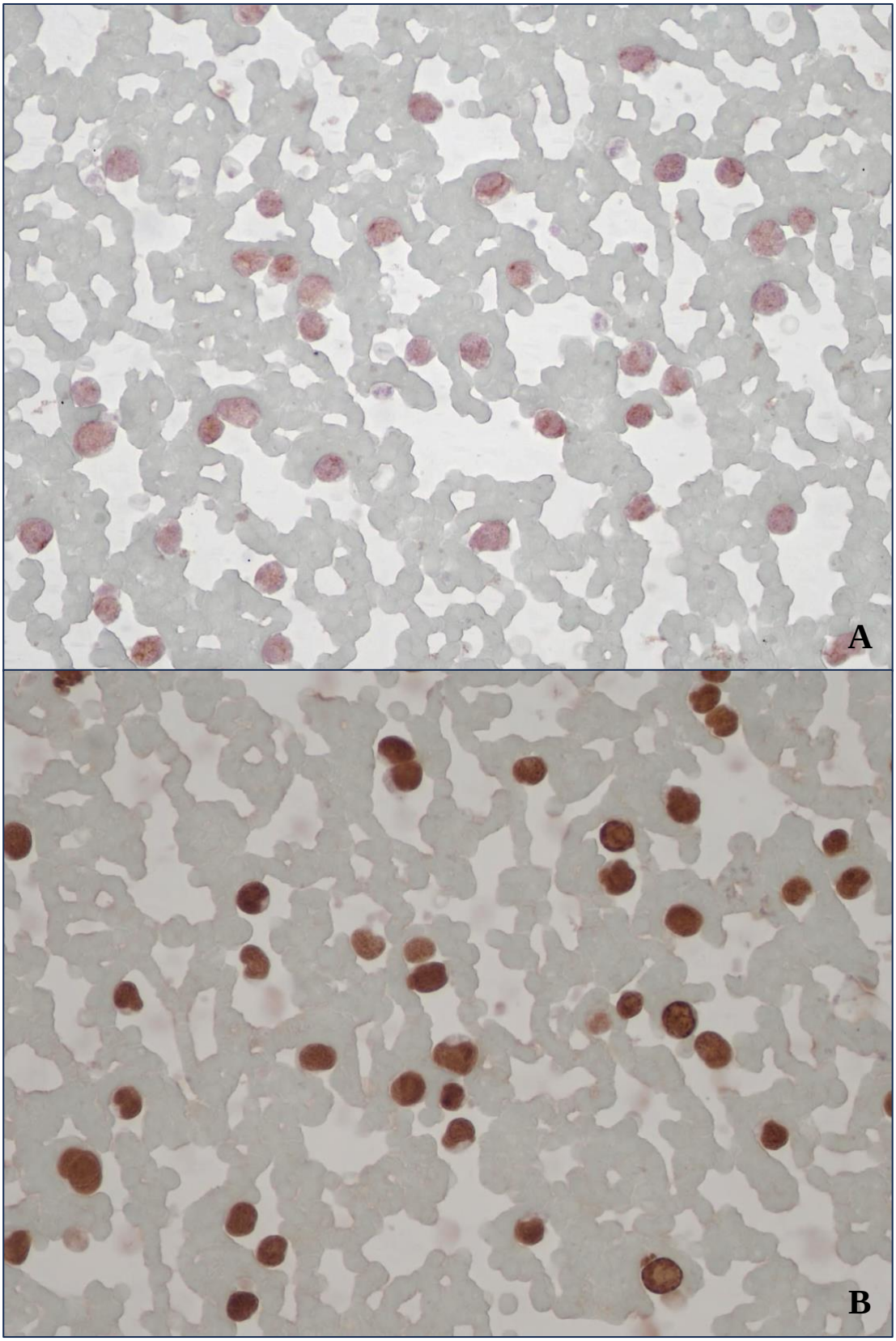

Figure 4: Immunocytochemistry results from the blood smear, showing over 80% of the atypical population displaying faint cytoplasmic/membrane CD3 staining (A) and more than 95% exhibiting positive Ki67 expression (B). 40x objective. Diaminobenzidine chromogen with hematoxylin counterstain.

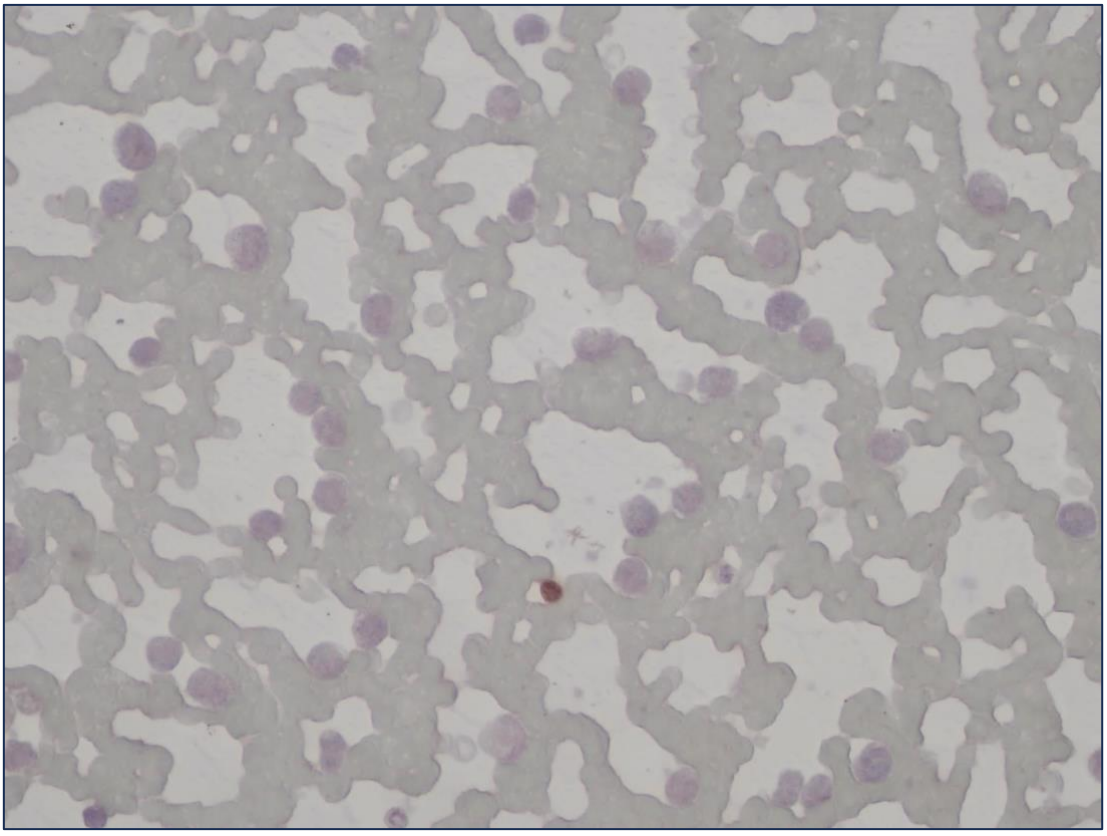

Figure 5: Immunocytochemistry results from the blood smear, demonstrating negative Pax5 marker expression in the atypical cells, with only rare small lymphocytes showing positive staining. 40x objective. Diaminobenzidine chromogen with hematoxylin counterstain.

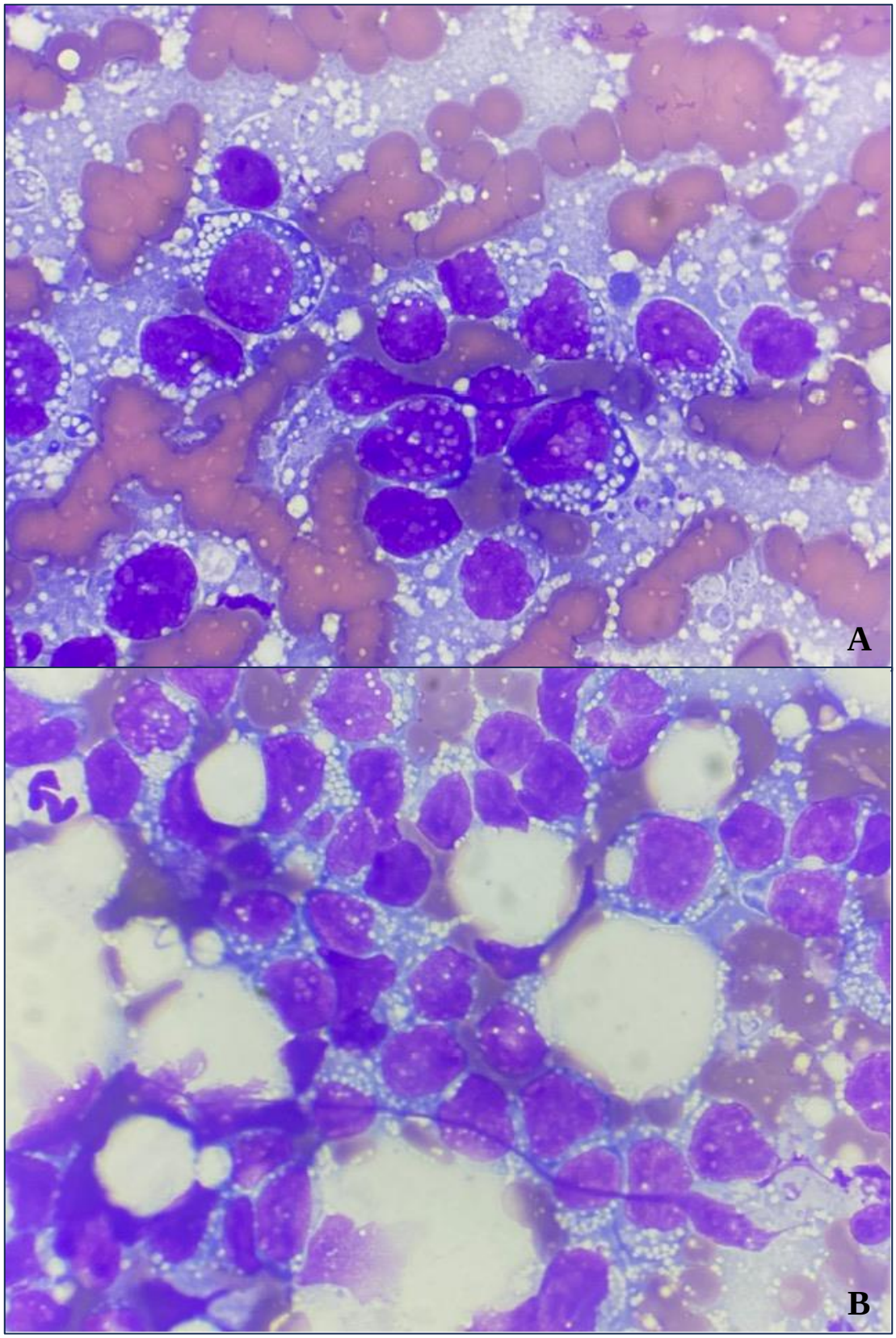

Figure 6: Fine needle aspiration from the right lateral thigh nodule showing the predominant cell population present. Hemacolor™, 100x (Oil immersion) objective.

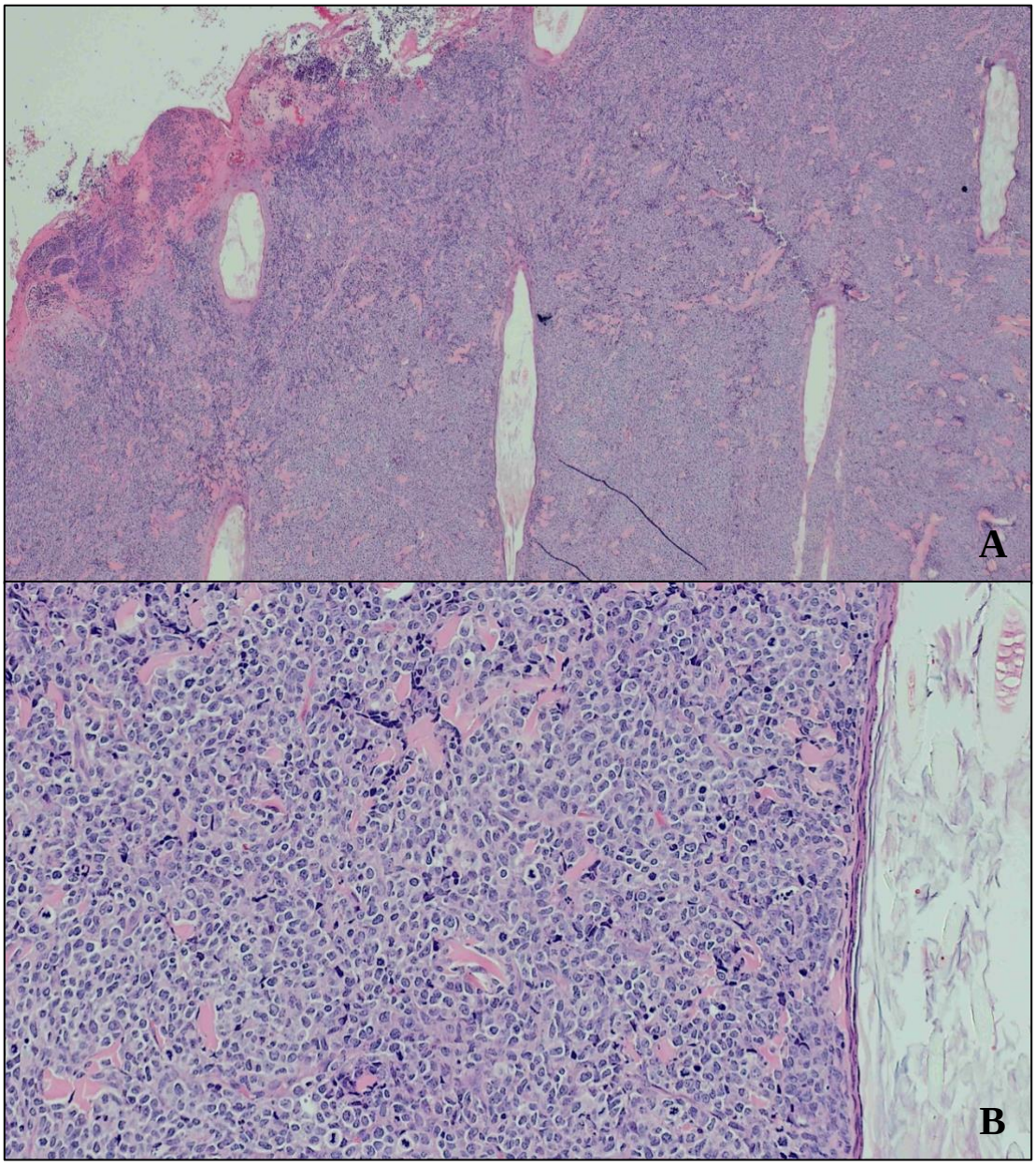

Figure 7: Histopathology from the right lateral thigh cutaneous nodule showing a packed neoplastic population of round cells without evidence of epitheliotropism (A) and surrounding a hair follicle (B). Haematoxylin and Eosin, 4x and 20x objectives, respectively.

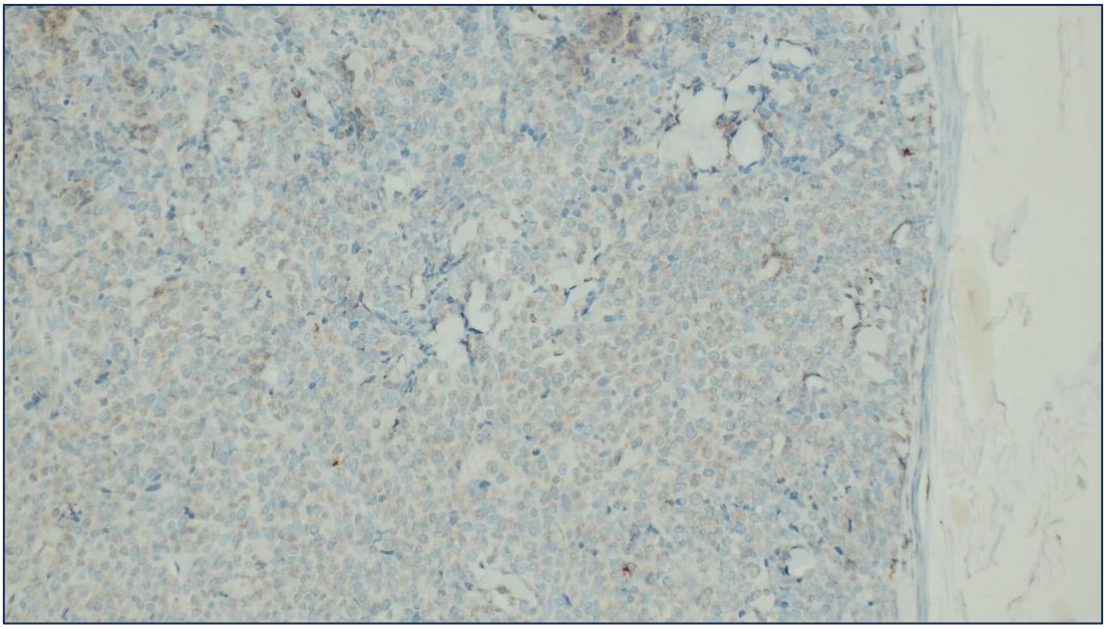

Figure 8: Immunohistochemistry results on a section of the right lateral thigh skin nodule, displaying a variable and mainly faint CD3 staining. 20x objective. Diaminobenzidine chromogen with hematoxylin counterstain.

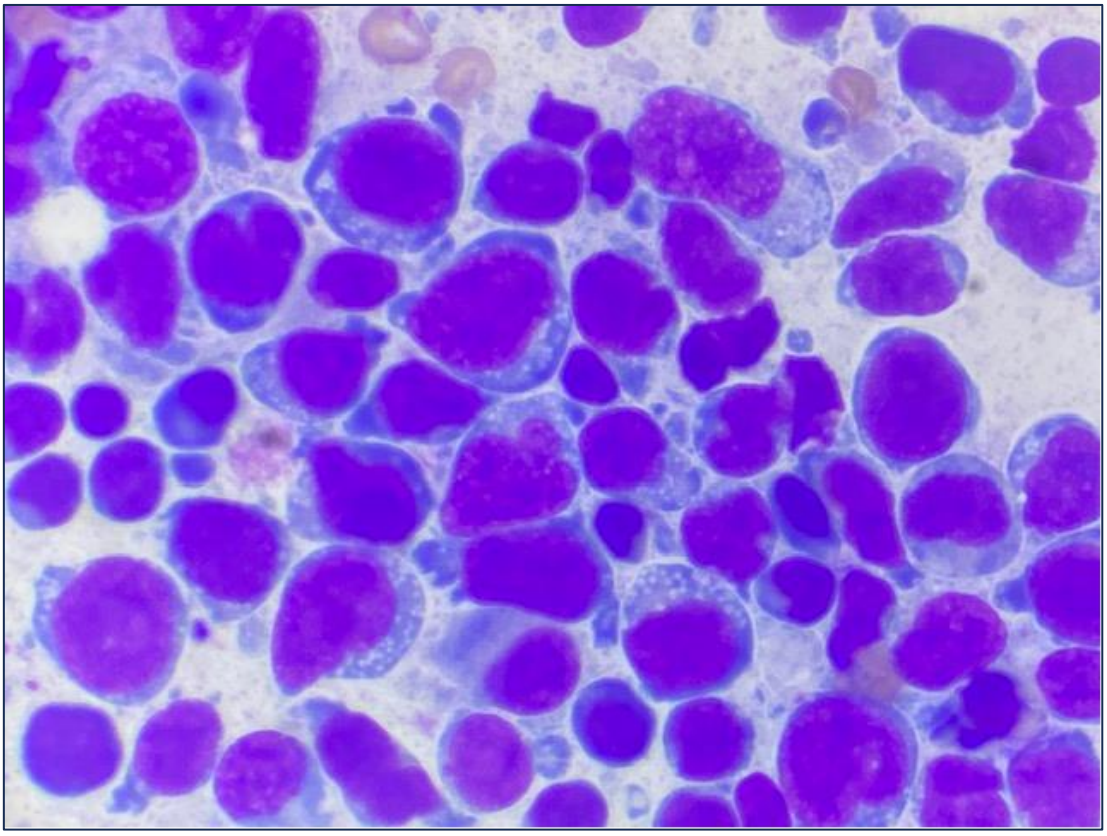

Figure 9: Fine needle aspiration from the right prescapular lymph node showing a predominance of an undetermined round cell population. Hemacolor™, 100x (Oil immersion) objective.

Follow-up and clinical outcome:

One week following the initial appointment, the clinical presentation of the previously described skin lesion underwent rapid evolution, characterised by heightened erythema and a shift to a doughnut shape (Figure 10), accompanied by the emergence of multiple small lesions and eruptions, including the ventral aspects of the base of the tail, caudoventral abdomen, head, ventral neck, and base of the ears. The manifestation of those new cutaneous lesions, alongside lethargy and mild hyporexia, prompted a referral to a specialised hospital for further evaluation.

At the referral hospital, clinical examination revealed moderate lymphadenomegaly affecting both mandibular lymph nodes and the right prescapular lymph node, and multiple firm, erythematous subcutaneous nodules were noted across various body regions (Figure 11). In-house cytology of the affected lymph nodes confirmed the presence of a round cell neoplasm (Figure 9), indicating systemic involvement. The blood results presented a mild leucocytosis due to neutrophilia (15.39 x 10^9/L [2.95-11-64 x 10^9/L]), mild thrombocytosis (495 x 10^9/L [148-484 x 10^9/L]) and a mild increase in ALP (284 IU/L [23-212 IU/L], with no evidence of atypical circulating cells on the blood smear. Further clinical staging, including imaging (thoracic radiography and abdominal ultrasound) and cytology from the spleen and liver, did not reveal significant abnormalities. This prompted the initiation of a CHOP chemotherapy protocol. Within one week of starting treatment, the patient exhibited clinical improvement and a partial response, characterised by normal lymph node size and reduction in the size of cutaneous lesions.

Subsequent diagnostic investigations, including histopathology and immunohistochemistry from the primary subcutaneous nodule, flow cytometry analyses from both the primary subcutaneous nodule and the ear mass, and PARR and immunocytochemistry from a previous stained blood smear, confirmed disseminated cutaneous lymphoma of T-cell lineage. However, upon identification of a large T-cell lymphoma, the treatment protocol was altered to a modified COEP, as per Elliot *et al.*[1], to include lomoustine. Remarkably, after the first lomoustine treatment, the patient achieved complete remission. Unfortunately, the remission was short-term, as multiple new cutaneous lesions (Figure 12), cytologically identical to the initial nodule, emerged mainly on the head and ventral abdomen shortly thereafter. Notably, lymph node size remained normal, and leucocyte blood counting remained normal (Table 3) with no atypical circulating cells noted on blood smear examination. Despite a rescue attempt with asparaginase showing no response, and subsequent administration of doxorubicin, the patient developed progressive disease, febrile neutropenia, and neurologic signs, including five seizure episodes within 24 hours. Ultimately, due to the progressive nature of the disease, the owner elected for euthanasia.

Table 3: Presentation of the last haematology results obtained using the ProCyte Dx haematology analyser. RI = Reference intervals.

	Results	RI	Units
ERITHROGRAM			
RBC	↓ **3.76**	5.65-8.87	10^{12}/L
HGB	↓ **86**	131-205	g/L
HCT	↓ **0.26**	0.37-0.62	ratio
MCV	68.6	61.6-73.5	fL
MCH	22.9	21.1-25.9	Pg
MCHC	333	320-379	g/L
RDW	18.5	13.6-21.7	%
RETICULOCYTES	57.9	10.0-110-0	K/μL
% RETICULOCYTES	1.5		%
RETICULOCYTE HAEMOGLOBIN	28.9	22.3-29.6	Pg
PLATELETS	↓ **144**	148-484	10^9/L
MPV	17.1	8.7-13.2	fL
LEUCOGRAM			
LEUCOCYTES	11.27	5.05-16.76	10^9/L
NEUTROPHILS	7.92	2.95-11.64	10^9/L
% NEUTROPHILS	70.2		%
LYMPHOCYTES	1.14	1.05-5.10	10^9/L
% LYMPHOCYTES	10.1		%
MONOCYTES	↑ **2.17**	0.16-1.12	10^9/L
% MONOCYTES	19.3		%
EOSINOPHILS	↓ **0.02**	0.06-1.23	10^9/L
% EOSINOPHILS	0.2		%
BASOPHILS	0.02	0.00-.0.10	10^9/L
% BASOPHILS	0.2		%

Notes: Platelet number confirm with dot plot and/or blood film review. Immature and/or toxic neutrophils likely present - consider inflammation. Anaemia without reticulocytosis – likely non-regenerative anaemia; consider pre-regenerative anaemia.

Figure 10: Macroscopic appearance of the right lateral thigh skin nodule at the referral hospital presentation.

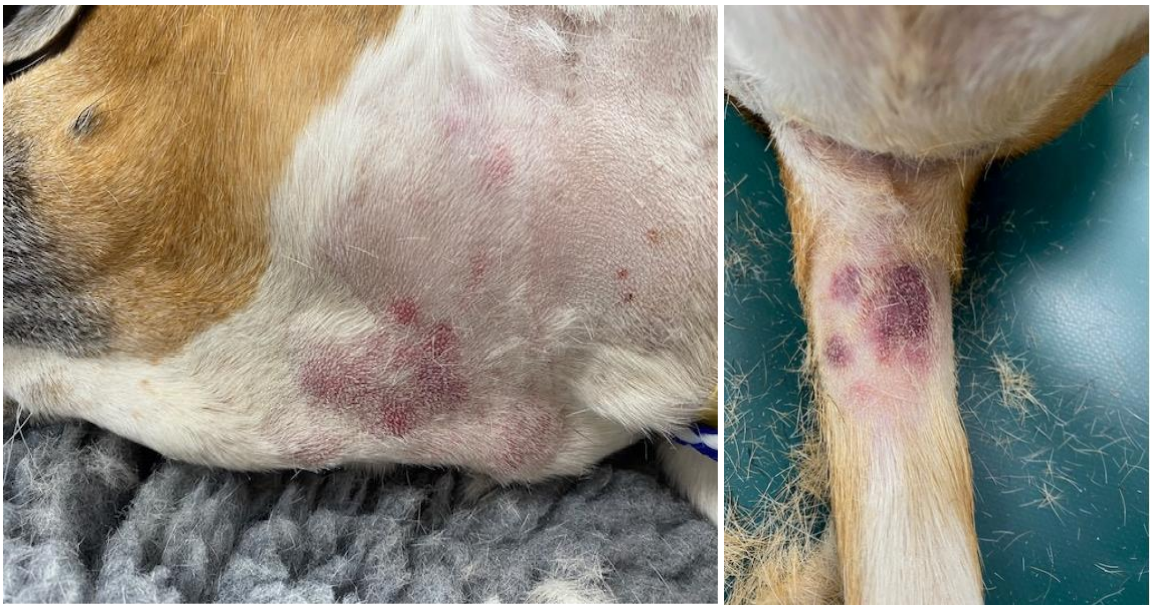

Figure 11: Macroscopic appearance of multiple firm, erythematous subcutaneous nodules observed across various body regions during the presentation at the referral hospital.

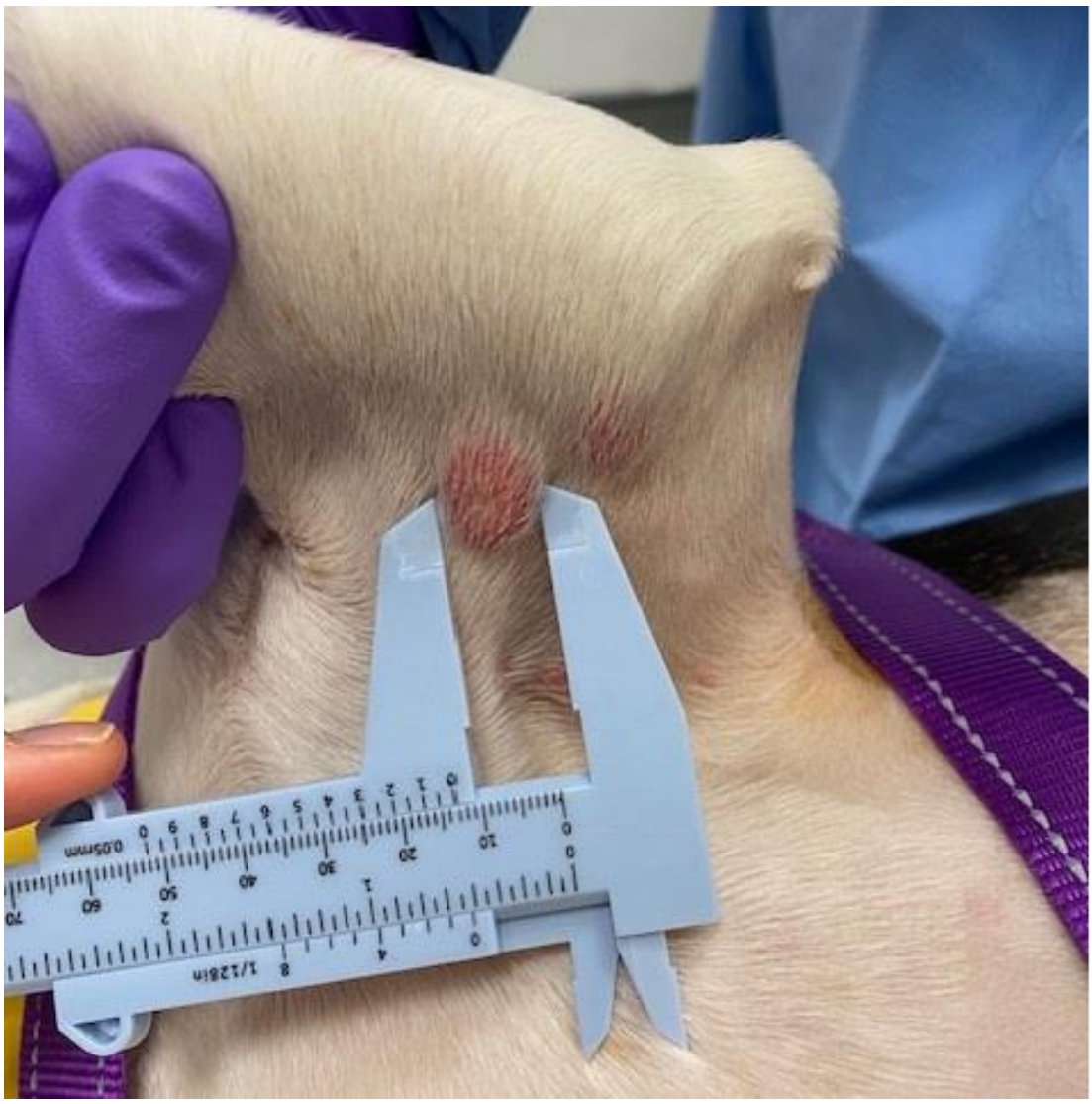

Figure 12: Macroscopic appearance of the new emergent cutaneous lesions at the referral hospital presentation.

Discussion:

(Considering the initial scattergram and blood smear findings, what differential diagnoses would you propose for the haematological results?)

The identification of a pronounced leucocytosis, characterised by the presence of large round abnormal cells, prompted immediately a comprehensive investigation. The analysis of Sysmex XN-V analyser scattergrams revealed discrepancies in cell enumeration accuracy, suggesting potential inaccuracies in the differential counting process. The inconsistent classification of atypical cells spanning basophil, neutrophil, and monocyte categories, through manual differential counting, mirrors findings previously reported[2]. In the study by Grebert et al, a similar discrepancy was noted, where abnormal cells were distributed across neutrophil, lymphocyte, and monocyte regions on the scattergram, utilizing the same haematology analyser, in a case of acute lymphoid leukaemia[2]. In our case, these aberrant cells were also noted within the basophilic region, with no discernible distribution through the lymphocytic area. This distribution pattern may be attributed to the cells' large size,

presence of cytoplasmic vacuoles, and fine pink cytoplasmic granulation. Although flow cytometry was not performed in this blood sample, a presumptive diagnosis of acute undifferentiated leukaemia (AUL) was made, due to the presence of more than 20% of blast cells in the peripheral circulation[3].

(How would you correlate the cytological findings of the skin nodule with the initial haematological blood results?)

Subsequently, cytological examination of the nodule on the patient's lateral right thigh revealed features consistent with a round cell neoplasia. The presence of identical cells observed on both the initial blood smear and the skin nodule raised suspicions regarding a common origin. Further diagnostic tests provided additional evidence of the shared origin of the transient cells observed on the blood smear and the cutaneous lesions. While PARR confirmed the presence of a monoclonal population, indicative of neoplasia, in the initial blood smear, the immunocytochemistry of a previous stained blood smear and immunohistochemistry of the primary nodule both suggested T-cell lymphoma. These findings established that the atypical cells transiently observed in the bloodstream and those in the primary nodule consisted with a monoclonal proliferation of neoplastic lymphoid T-cells, supporting a common origin.

(What are the possible explanations for the disappearance of the haematological abnormalities in the second blood sample?)

Several possible explanations were considered for the subsequent unremarkable blood haematology results with no circulating atypical cells, two weeks after initial presentation, in particular a transient leukaemia, especially as no chemotherapy or glucocorticoid treatment was administered. Initially, the possibility of sample swapping between patients was considered and quickly dismissed after confirming the correct patient sample with the clinician and observing similar red blood cell parameters between samples. This was further supported by the similar morphological and immunophenotyping features between the atypical cells in bloodstream and the neoplastic round cells found on the skin nodule. Secondly, the possibility of percutaneous cell aspiration during blood collection was also dismissed since the sample was obtained from the jugular vein and, at that point, no neck masses were present. The remaining possibilities still plausible include the transient passage of these cells from the nodule through the bloodstream, leading to the subsequent appearance of multiple nodules on the cutaneous surface, or the immune system's destruction of circulating neoplastic cells. While the transient leukaemia phenomenon is not yet described in veterinary medicine, it has been occasionally reported in human medicine, particularly in acute lymphoblastic leukaemia (ALL) cases[4–6]. The underlying mechanisms remain elusive; however, the immune system is thought to play a crucial role in these cases. In human medicine, spontaneous remissions in ALL often occur following a presentation of fever, sepsis, or acute stress-inducing conditions[5]. Previous studies have reported a variable remission time ranging from 5 days to 7 weeks, with almost all cases experiencing a relapse with a blast phenotype similar to the one reported at presentation[5,6]. Notably,

our patient exhibited mild hyperthermia during the initial clinical presentation, and no medical treatment was prescribed, suggesting the potential involvement of the inflammatory system, as previously described in human cases. However, no signs of leukaemic relapse were observed, likely attributable to the initiation of chemotherapy treatment or the patient's abbreviated lifespan, which may not have afforded adequate time to observe this phenomenon.

Additionally, the absence of bone marrow aspiration and biopsy, in this case, does not entirely rule out the possibility of bone marrow infiltration from the T-cell lymphoma or primary T-cell leukaemia, potentially presenting as aleukemic leukaemia. However, this scenario seems less likely, given the observed progression from a leukemic to an aleukemic state without medical intervention and the absence of cytopenias in haematopoietic lineages. Typically, acute leukaemias present with moderate to severe nonregenerative anaemia and thrombocytopenia, which were not observed here[3,7]. Only moderate thrombocytopenia was initially noted during the transient leukaemia phase, followed by a shift to mild thrombocytosis.

Canine cutaneous lymphoma is classified into epitheliotropic and non-epitheliotropic subtypes based on histological assessment and lymphocyte location[8]. Non-epitheliotropic lymphoma can develop as cutaneous and/or subcutaneous nodules or plaques. While canine epitheliotropic lymphoma is almost always of T -cell origin, the non-epitheliotropic form can be both T and B cell origin. Cutaneous non-epitheliotropic lymphoma is rare in both humans and dogs. Further subclassification according to the WHO classification is uncommonly performed in canine T-cell non-epitheliotropic lymphoma, as was the case here[9]. Based on available data prognosis for non-epitheliotropic cutaneous lymphoma is generally guarded, and the median survival period is 1-36 months[10,11]. Due to the rarity of the disease and scarce information regarding response to the treatment, the dog was treated with a modified CHOP protocol reported as a treatment for high-grade T cell lymphoma in dogs[1]. Despite a good initial response (achieving maximal response within 22 days), relapse occurred after 36 days, with an overall survival time of 55 days.

In summary, to the authors' knowledge, this case represents the first documented case report of transient acute T-cell lymphoid leukaemia likely originating from an underlying primary cutaneous T-cell lymphoma. The scarcity of previous cases can be attributed to the challenge of identifying this transient leukaemia, which is compounded by its indefinite duration, the absence of specific associated signs, and the necessity of integrating haematology examinations with blood smears in cases of leucocytosis to accurately identify the atypical circulating cells. Additionally, the rarity of such occurrences, as observed in human medicine, further contributes to the limited documentation. This case underscores the importance of combining manual examination with automated analysis to achieve precise diagnoses, particularly in haematological malignancies where discrepancies in identifying abnormal cells are common. This case also highlights the importance of immunophenotyping, as cytological features alone can be misleading. In this instance, the cells

exhibited large size, variable nuclear contours, delicate chromatin patterns, cytoplasmic vacuoles, and mild granulation, possibly leading to misclassification as acute myeloid leukaemia (AML)[3].

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