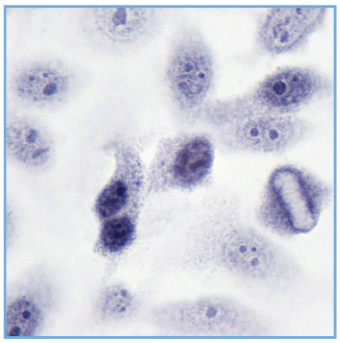
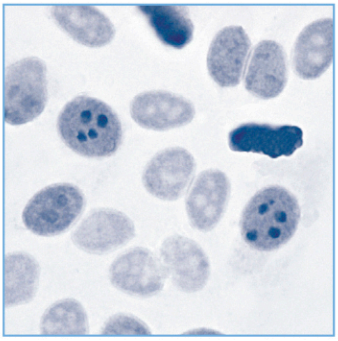
Colorzyme®
Patterns

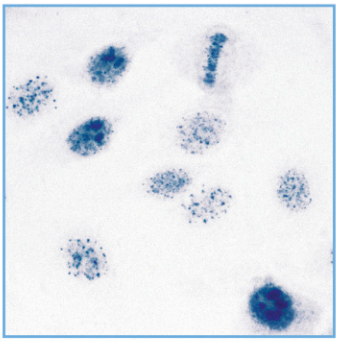
Associated with Antinuclear Antibody Detection



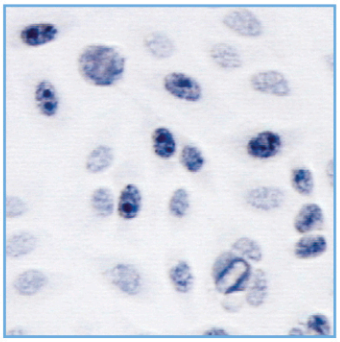
Nucleolar and SSA/Ro



Homogeneous and SSA/Ro



Centromere and SSA/Ro



SSA/Ro

immuno concepts®

Antigen Chart

Associated with ANA Patterns

Pattern observed	Type of antibody	Disease(s) in which antibodies are seen	Characteristics of antigenic determinants	Routine tests used to confirm specific antibody
Homogeneous	Double-stranded DNA (nDNA, dsDNA)	Characteristic of SLE, lower levels in other rheumatic diseases	Double-stranded DNA	IFA or CZ using *Crithidia luciliae*, RIA, ELISA
	Nucleosome or Chromatin	SLE, Drug-induced LE	DNA-histone complex	ELISA
	Histone	Drug-induced LE, SLE	Different classes of histone	ELISA
Unusual Homogeneous	Nuclear Membrane	Lupoid hepatitis	Nuclear Lamins A, B, C and gp210	ELISA for gp-210
Speckled	Sm (Smith)	Marker antibody for SLE	Proteins B'/B, D, E, F, and G complexed with U1, U2, U4, U5, U6, U7, U11, U12 RNP	Immunodiffusion (ID), ELISA
	U1-RNP	High levels in MCTD and SLE, low levels in other rheumatic diseases	70 kDa, A and C proteins complexed with U1 RNP	ID, ELISA
Speckled (and/or SSA pattern if using HEp-2000®) Can also be ANA negative	SS-A/Ro	High prevalence in Sjögren's syndrome sicca complex, lower prevalence in other rheumatic diseases	60 kDa protein complexed with hY RNA's	Confirmatory with HEp-2000® staining pattern, confirm with ID, ELISA
Fine Speckled or ANA negative	Ro52	Sjögren's syndrome, myositis, Neonatal Lupus	52 kDa protein	ELISA
Fine Speckled (sometimes with nucleolar staining as well)	SS-B/La	High prevalence in Sjögren's syndrome sicca complex, lower prevalence in other rheumatic diseases	48 kDa protein complexed with RNA polymerase III	ID, ELISA
Fine Speckled, Homogeneous, Nucleolar	Scl-70	Marker antibody for Scleroderma	100 kDa proteins of topoisomerase I	ID, ELISA
Cell Cycle Dependent Speckled	PCNA	Marker antibody for SLE	Auxiliary protein to DNA polymerase ∂	ID, ELISA
Coarse Speckled	Nuclear Matrix	Seen in some patients with evolving connective tissue disease	hnRNP and other antigens	None
6-20 dots	NSp I, sp-100, MND, PBC 95	Associated with Primary Biliary Cirrhosis	95-100 kDa protein	ELISA
Cell Cycle Dependent Speckled with speckling in metaphase mitotics	NSp II, CENP F	Some association with malignancies	400 kDa protein	None
Staining in cleavage furrow between dividing cells	Midbody	Unknown	Unknown	Confirm by staining pattern
1-5 dots	p80 (coilin)	Unknown	80 kDa protein in the coiled body	None
Centromere	Centromere	Seen in 57-82% of patients with limited form (CREST) of Scleroderma and Raynaud's phenomenon	CENP A, CENP B, CENP C	Confirmed by staining pattern, ELISA
Nucleolar	Clumpy Nucleolar	Scleroderma	Fibrillarin	ELISA
	Speckled Nucleolar	Scleroderma and other connective tissue diseases	RNA polymerase I, NOR-90, others?	ELISA
	Smooth Nucleolar	Polymyositis/Scleroderma overlap	PM-1 (PM/Scl), others?	ELISA

Systemic Rheumatic Disease

Identification of the antinuclear antibody (ANA) pattern remains a crucial step in the process of diagnosing the systemic rheumatic diseases. ANA patterns often give the clinician insight into which autoantibodies are present and indications of disease likelihood.

It has now been over 60 years since the LE cell was first described by Hargraves (1). During this time, substantial improvements in physician awareness, diagnostics and treatments have increased the survival rate for lupus patients from a 5 year rate of only 50% to a 10 year rate of >90% (2).

There is growing evidence that the appearance of autoantibodies may precede the onset of the disease, often by many years. Early detection of these autoantibodies may offer the opportunity for earlier diagnosis and treatment, improving the length and quality of life for the patient.

A recent study in the New England Journal of Medicine reported that, on average, at least one antinuclear antibody was present 3 years prior to the clinical diagnosis of SLE being made and at the time of diagnosis there were often 3 autoantibodies present (3). The earliest antibodies detected were ANA's, anti-SSA/Ro and anti-SSB/La antibodies. These antibodies were readily detected and reported using the HEp-2000® slide based assay.

The HEp-2000® substrate is Immuno Concepts' patented ANA substrate that has been consistently proven in independent studies to be superior to standard HEp-2 for the detection and identification of ANA's (4-7). When the unique SSA/Ro pattern is present on the HEp-2000® substrate the laboratory can immediately report the presence of anti-SSA/Ro antibodies to the clinician, potentially accelerating the correct diagnosis for the patient.

The photographs and charts presented here are designed to give the laboratorian a comprehensive guide to pattern recognition, antigen specificity, and disease association. Some of the more recently described patterns do not have disease association but are included for educational value.

References:

1 Hargraves, M., Richmond H., et al., Presentation of two bone marrow components, the tart cell and the LE cell. Mayo Clin Proc. 1948;27:25-28.

2 Alamanos, Y., Voulgari, P.V., et al., Survival and mortality rates of systemic lupus erythematosus patients in northwest Greece. Study of a 21-year incidence cohort. Rheumatology. 2003;42(9):1122-1123.

3 Arbuckle, M. R., McClain, M. T. et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. New England Journal of Medicine. 2003;349(16):1526-1533.

4. Pollock W, Toh BH. Routine immunofluorescence detection of Ro/SS-A autoantibody using HEp-2 cells transfected with human 60 kDa Ro/SS-A. J.Clin.Pathol. 1999;52:684-687.

5. Bossuyt X, Meurs L., et al., Screening for autoantibodies to SS-A/Ro by indirect immunofluorescence using HEp-2000® cells. Ann Clin Biochem. 2000;37:216-219.

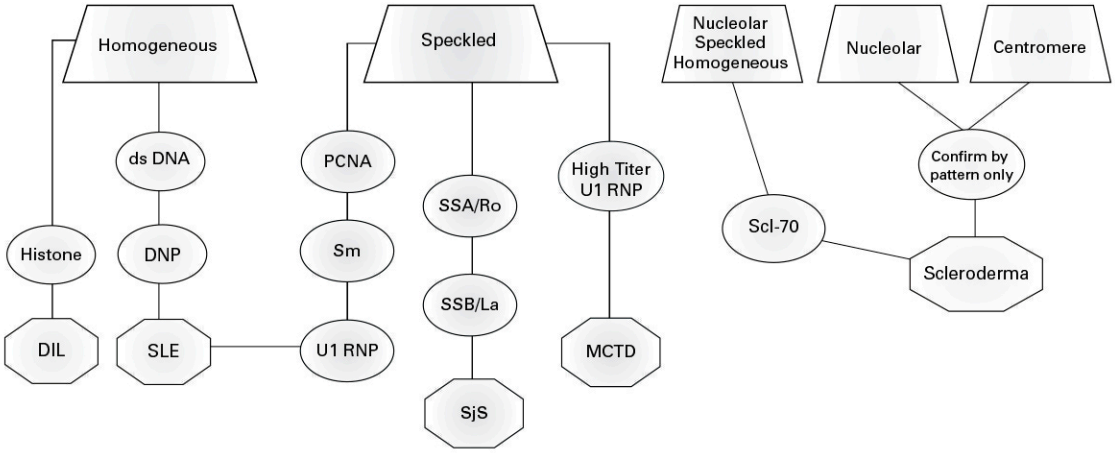
6. Fritzler MJ, Hanson C., et al., Specificity of autoantibodies to SS-A/Ro on a transfected and overexpressed human 60 kDa Ro autoantigen substrate. J.Clin.Lab.Anal. 2002;16:103-108.

7. Bossuyt X, Frans J., et al. Detection of Anti-SSA Antibodies by Indirect Immunofluorescence. Clin Chem. 2004;50(12):2361-2369.

Flow Chart

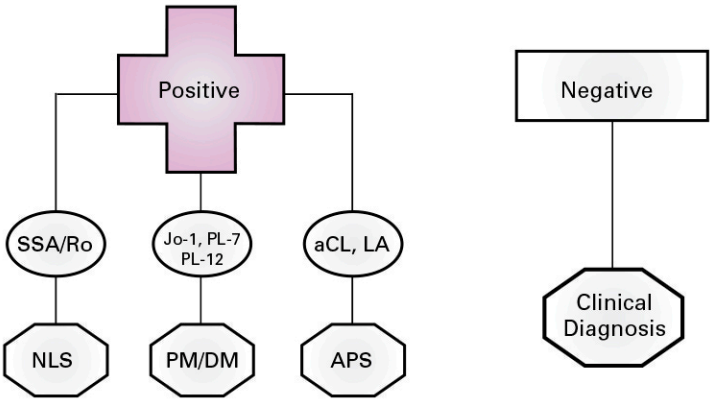
ANA Pattern Confirmatory Testing & Disease Association

ANA Positive



ANA Negative

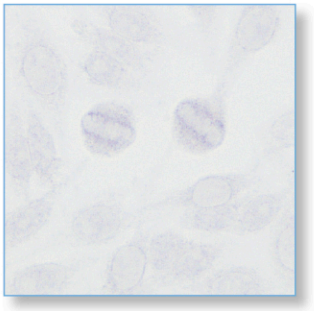
If the ANA is negative, but disease is suspected, test for specific autoantibodies



Legend

DIL - Drug induced lupus
SLE - Systemic lupus erythematosus
SjS - Sjögren's syndrome
MCTD - Mixed connective tissue disease
Pm/Dm - Polymyositis / Dermatomyositis
APS - Antiphospholipid syndrome
NLS - Neonatal lupus syndrome

Negative 1



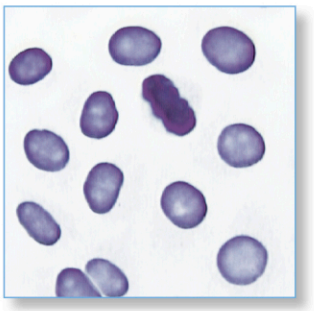
Report as: ANA Negative

Suspected antigen specificity: None

Clinical significance: None.

Follow-up testing: None required.

Homogeneous 2



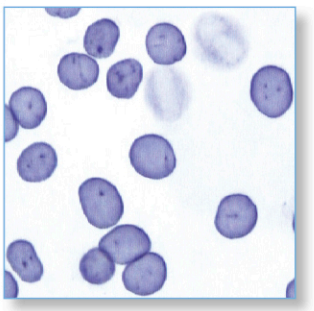
Report as: Homogeneous

Suspected antigen specificity: nDNA, DNP, Histone, DNA binding proteins, others?

Clinical significance: nDNA positive - marker antibody seen in 60% of SLE patients.

Follow-up testing: Confirm nDNA antibodies.

Nuclear Membrane 3



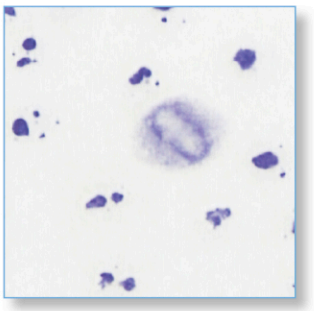
Report as: Nuclear Membrane

Suspected antigen specificity: Nuclear lamins, others?

Clinical significance: May be seen in patients with SLE, RA, autoimmune hepatitis.

Follow-up testing: None required.

Nucleolar (clumpy) 4



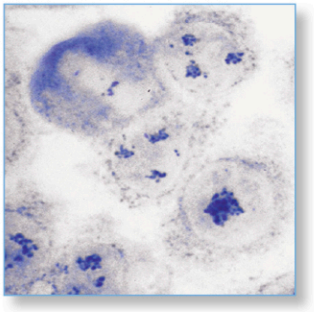
Report as: Nucleolar

Suspected antigen specificity: Fibrillarin, others?

Clinical significance: Seen in patients with systemic sclerosis.

Follow-up testing: None required.

Nucleolar (speckled) 5



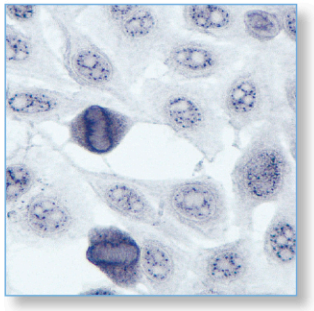
Report as: Nucleolar

Suspected antigen specificity: RNA Polymerase I, NOR 90, others?

Clinical significance: Seen in patients with diffuse scleroderma.

Follow-up testing: None required.

Nuclear Matrix 6



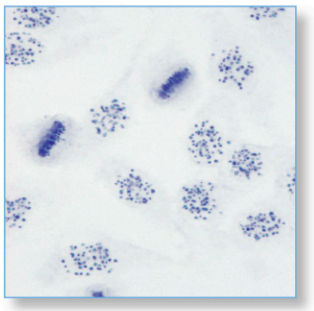
Report as: Speckled

Suspected antigen specificity: hnRNP, others?

Clinical significance: Seen in patients with evolving rheumatic diseases.

Follow-up testing: ENA testing to rule out specific ENAs.

Centromere 7



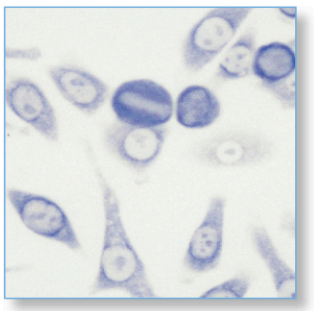
Report as: Centromere

Suspected antigen specificity: Centromere protein A, B, or C

Clinical significance: Seen in 57–96% of patients with the limited form of scleroderma (CREST).

Follow-up testing: None required. Staining pattern confirms presence of ACA.

suspect Ribosomal P 8



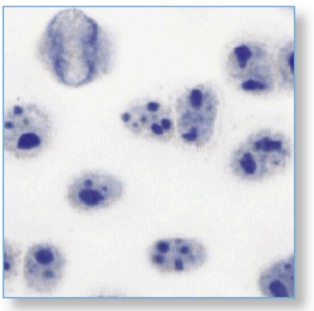
Report as: Nucleolar, suspect Ribosomal P

Suspected antigen specificity: Ribosomal P proteins P0, P1, and P2

Clinical significance: Seen in up to 20% of patients with SLE.

Follow-up testing: Confirm with anti-ribosomal specific assay.

Nucleolar (smooth) 9



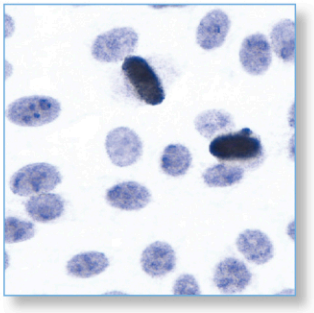
Report as: Nucleolar

Suspected antigen specificity: Pm/Scl

Clinical significance: Seen in patients with polymyositis/ scleroderma overlap.

Follow-up testing: None required.

Scl-70 10



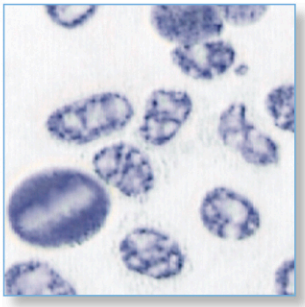
Report as: Homogeneous, Speckled, and Nucleolar

Suspected antigen specificity: Topoisomerase I

Clinical significance: Topoisomerase I positive - marker antibody seen in 15–20% of patients with scleroderma.

Follow-up testing: Confirm by ENA testing.

Speckled 11



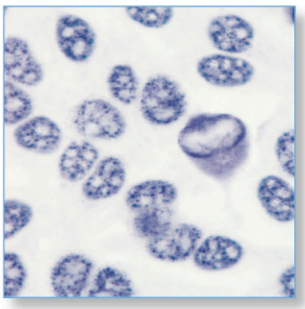
Report as: Speckled

Suspected antigen specificity: Sm, U1-RNP, others?

Clinical significance: Sm positive - marker antibody seen in 4–40% of SLE patients. RNP positive - seen in high titers in patients with MCTD and SLE, low titers in other diseases.

Follow-up testing: ENA testing to rule out specific ENAs.

Coarse Speckled 12



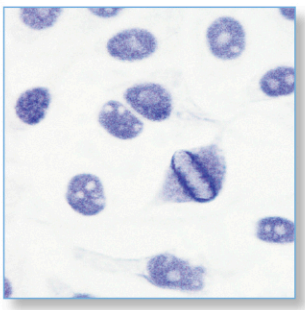
Report as: Speckled

Suspected antigen specificity: U1-RNP, others?

Clinical significance: Sm positive - marker antibody seen in 4–40% of SLE patients. RNP positive - seen in high titers in patients with MCTD and SLE, low titers in other diseases.

Follow-up testing: Confirm by ENA testing.

Speckled (flat or fine) 13



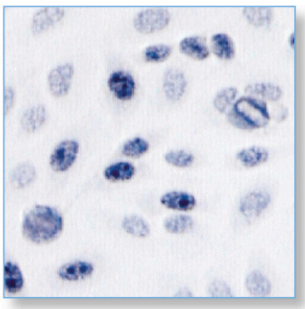
Report as: Speckled

Suspected antigen specificity: SSA/Ro, SSB/La, others?

Clinical significance: SSA/Ro and SSB/La positive - seen in high percentage of patients with primary Sjögren's syndrome, 30–40% of patients with SLE.

Follow-up testing: Confirm by ENA testing.

HEp-2000® 200x 14

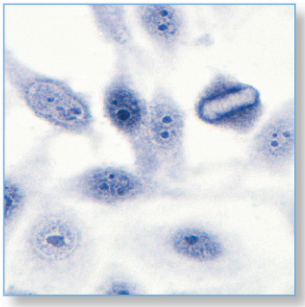


Report as: SSA/Ro

Suspected antigen specificity: SSA/Ro

A distinct speckled and nucleolar pattern seen in 10–20% of the interphase nuclei. These are the hyperexpressing cells. The remaining 80-90% of the interphase cells may or may not demonstrate staining. The chromosome region of the metaphase mitotic cells is negative.

HEp-2000® 400x 15



Report as: SSA/Ro

Suspected antigen specificity: SSA/Ro

Clinical significance: SSA/Ro positive - seen in 60-70% of patients with primary Sjögren's syndrome, 30–40% of patients with SLE.

Follow-up testing: This pattern is confirmatory for SSA/Ro antibodies. Suggest ENA testing to rule out the presence of antibodies to other ENAs.

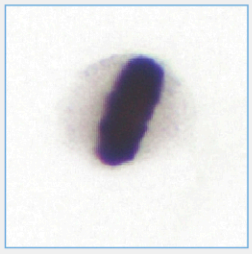
Colorzyme® Patte

Associated wi Antib

Mitosis

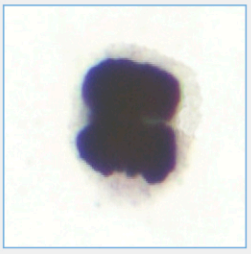
Stages of Cell Division

Metaphase



The double-stranded chromosomes align at the center of the cell and the spindle fibers (generated from the centrioles) attach to the centromeres. Because the nuclear membrane has dissolved, nonchromosome specific antigens redistribute to outer region of the cell.

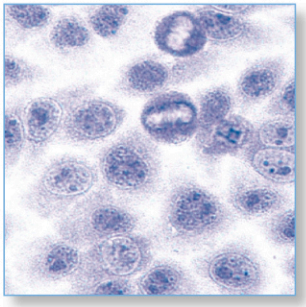
Anaphase



Chromosomes move to opposite poles.

Tech Support 800-251-5115

Speckled & Nucleolar 16



(SSA/SSB on regular HEp-2)

Report as: Speckled and Nucleolar

Suspected antigen specificity: SSA/Ro, SSB/La, others?

Clinical significance: SSA/Ro positive - see previous pattern. SSB/La positive - seen in 50-60% of patients with primary Sjögren's syndrome and 10-15% of SLE patients. Also seen in conjunction with SSA/Ro in patients with neonatal lupus.

Follow-up testing: Confirm by ENA testing.

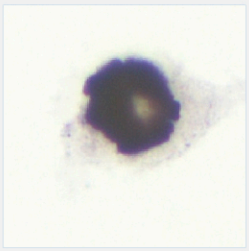
terns

with Antinuclear ntibody Detection

Interphase

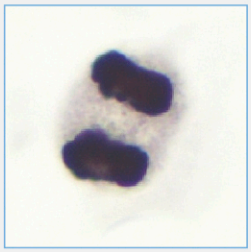
DNA synthesis and chromosome replication occurs. Centrioles replicate.

Prophase



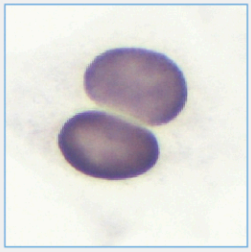
Chromosomes condense. Centrioles migrate to opposite ends of the cell. Nuclear membrane fragments.

Telophase



Spindle dissolves and nonchromosome specific antigens become contained within the chromosomal matrix as the nuclear membrane reforms.

Cytokinesis



Cell division is complete.

Note: chromosome staining demonstrated utilizing DNA specific antibody.

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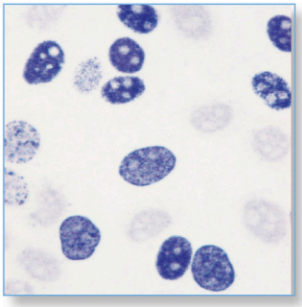
PCNA 17



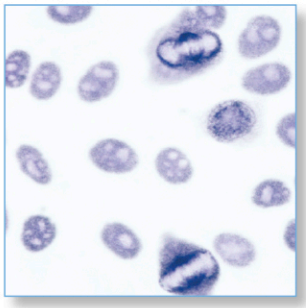
Report as: Speckled, suspect PCNA

Suspected antigen specificity: DNA polymerase ∂ (cyclin)

Clinical significance: PCNA positive: marker antibody seen in 2–10% of SLE patients.

Follow-up testing: Confirm by ENA testing.

NuMA 18



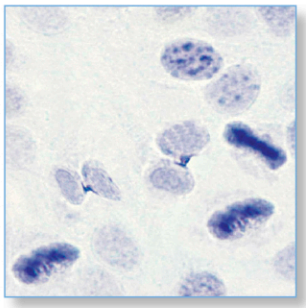
Report as: Speckled, mitotic spindle also present

Suspected antigen specificity: Nuclear Mitotic Apparatus

Clinical significance: Sjögren's Syndrome, PBC, others?

Follow-up testing: ENA testing to rule out specific ENAs.

Midbody 19



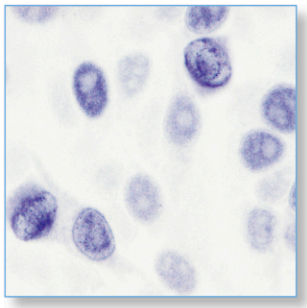
Report as: Atypical speckled, Midbody

Suspected antigen specificity: Midbody

Clinical significance: May be seen in a low percentage of patients with scleroderma.

Follow-up testing: None required, confirmed by staining pattern.

NSp II 20



NSp II (CENP F)

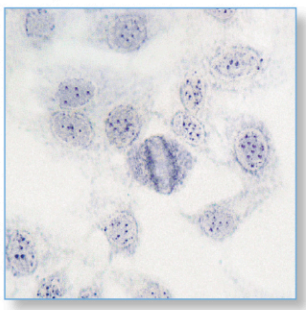
Report as: Atypical speckled, suspect NSp II

Suspected antigen specificity: Centromere protein "F", others?

Clinical significance: Unknown, some association with malignancies.

Follow-up testing: None required.

Multiple Nuclear Dots 21



Multiple Nuclear Dots (NSp I, PBC 95)

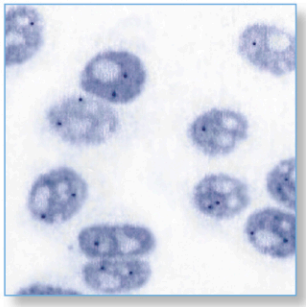
Report as: Atypical speckled, suspect Multiple Nuclear Dots

Suspected antigen specificity: 95 - 100 kD protein

Clinical significance: Seen in 27-44% of patients with PBC.

Follow-up testing: None required.

p80-coilin (1-5 dots) 22



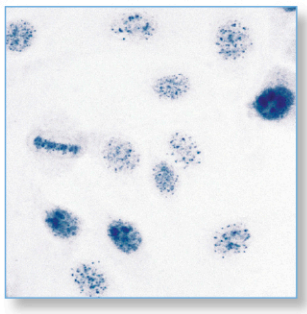
Report as: Atypical speckled, suspect p80-coilin

Suspected antigen specificity: Coilin

Clinical significance: Unknown.

Follow-up testing: None required.

Mixed ANA pattern 23



Mixed ANA pattern on HEp-2000®

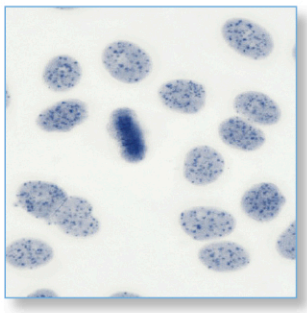
Report as: Centromere and SSA/Ro

Suspected antigen specificity: Centromere protein A, B, or C; SSA/Ro

Clinical significance: See significance for each respective pattern.

Follow-up testing: SSA/Ro confirmed by pattern. Centromere confirmed by pattern.

Mixed ANA pattern 24



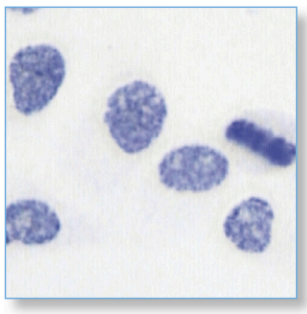
Mixed ANA pattern on HEp-2000®

Report as: Homogeneous and Centromere

Suspected antigen specificity: nDNA, DNP, Histone, DNA binding proteins, Centromere protein A, B, or C.

Clinical significance: Seen in systemic sclerosis patients with pulmonary disease.

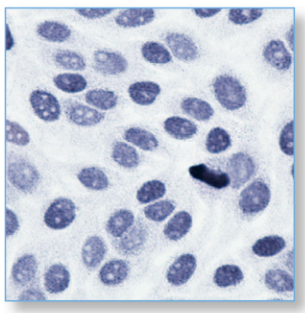
Mixed ANA pattern 25



Report as: Homogeneous and Speckled

Mixed ANA patterns can be caused by autoantibodies to several different antigens or by antibodies to an antigen located in several different areas of the cell nucleus. Titering and appropriate confirmatory testing for each pattern is recommended.

Mixed ANA pattern 26



Mixed ANA pattern on HEp-2000®

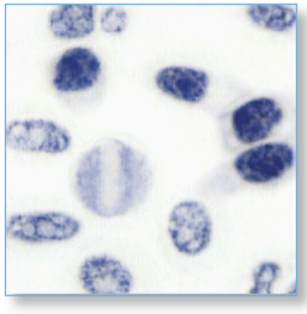
Report as: Atypical speckled or Cell Cycle Dependent Speckled and Homogeneous

Suspected antigen specificity: Unknown for atypical speckled pattern. See homogeneous antigen specificity.

Clinical significance: Unknown for cell cycle dependent speckled. See homogenous pattern for clinical significance.

Follow-up testing: ENA testing to rule out specific ENAs.

Mixed ANA pattern 27



Mixed ANA pattern on HEp-2000®

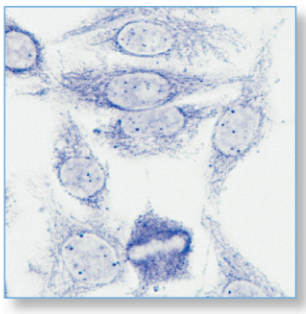
Report as: Speckled and SSA/Ro

Suspected antigen specificity: Sm, U1-RNP, SSA/Ro, SSB/La, others

Clinical significance: See significance for each respective pattern.

Follow-up testing: SSA/Ro antibodies confirmed by pattern. Confirm speckled pattern by ENA testing.

MND and AMA 28



Mixed ANA pattern on HEp-2000®

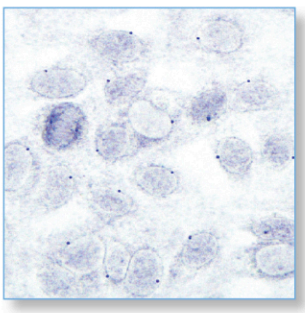
Report as: Atypical speckled, suspect Multiple Nuclear Dots (NSp1) and cytoplasmic speckling.

Suspected antigen specificity: 95-100 kD protein, mitochondria.

Clinical Significance: Seen in patients with primary billary cirrhosis.

Follow-up testing: None required.

suspect Centriole 29



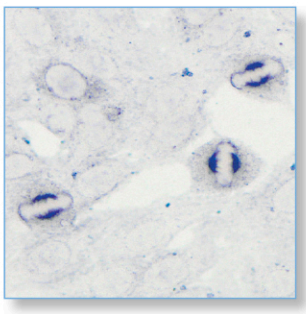
Report as: ANA Negative, suspect Centriole

Suspected antigen specificity: Centriole proteins

Clinical significance: Unknown.

Follow-up testing: None required.

Mitotic Spindle 30



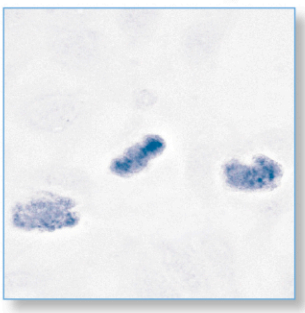
Report as: ANA Negative, Mitotic Spindle

Suspected antigen specificity: Mitotic spindles

Clinical significance: Seen in evolving rheumatic diseases.

Follow-up testing: None required.

Chromosomal Coating 31



Report as: ANA Negative, suspect Chromosomal Coating Antibody

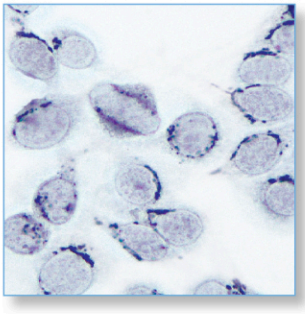
Pattern: Stains only the chromosomal area of metaphase cells

Suspected antigen specificity: Unknown

Clinical significance: Unknown.

Follow-up testing: None required.

suspect Golgi 32



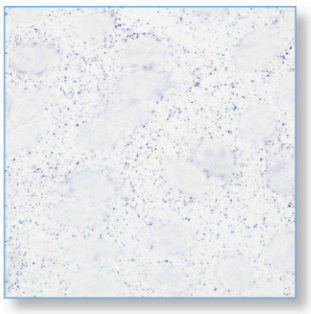
Report as: ANA Negative, suspect Golgi

Suspected antigen specificity: Golgi proteins

Clinical significance: Seen in patients with primary Sjögren's Syndrome and SLE.

Follow-up testing: None required.

suspect Jo-1 33



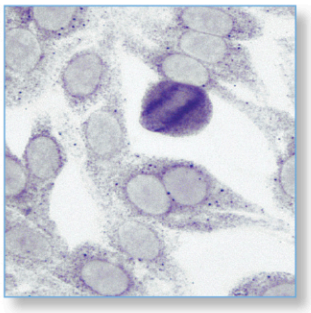
Report as: ANA Negative, cytoplasmic speckling

Suspected antigen specificity: Jo-1 (Histidyl tRNA synthetase)

Clinical significance: Seen in up to 35% of patients with myositis.

Follow-up testing: Confirm with Jo-1 specific testing.

suspect Endosomal/GWB 34



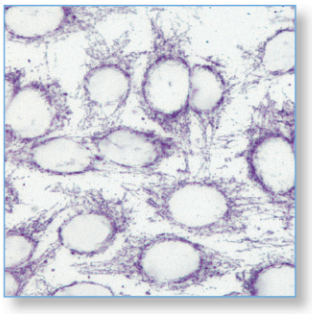
Report as: ANA Negative, cytoplasmic speckling

Suspected antigen specificity: EEA-1, GW182, GW2, GW3, Ge-1/Hedls, RAP55 proteins

Clinical significance: Unknown.

Follow-up testing: None required.

suspect Mitochondrial 35



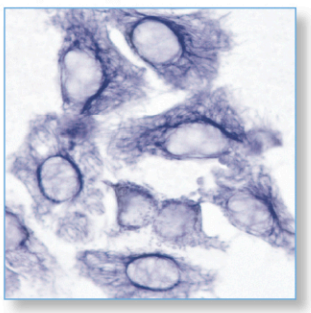
Report as: ANA Negative, suspect Mitochondrial

Suspected antigen specificity: Mitochondria

Clinical significance: Seen in up to 90% of patients with PBC.

Follow-up testing: Confirm on AMA specific substrate such as rodent tissue.

suspect Cytoskeletal 36



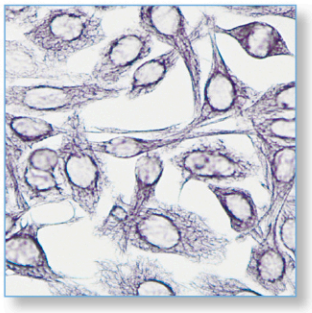
Report as: ANA Negative, suspect Cytoskeletal

Suspected antigen specificity: tubulin, vimentin, others?

Clinical significance: Seen in patients with autoimmune liver disease.

Follow-up testing: Confirm on antigen specific substrate such as rodent tissue.

suspect Cytoskeletal 37



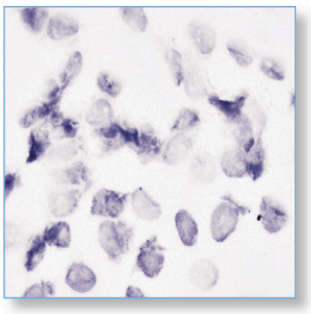
Report as: ANA Negative, suspect Cytoskeletal

Suspected antigen specificity: Actin.

Clinical significance: Seen in patients with autoimmune liver disease.

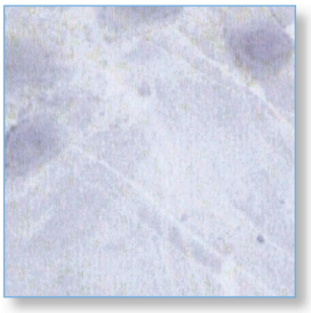
Follow-up testing: Confirm on antigen specific substrate such as rodent tissue.

Mechanical Damage 38



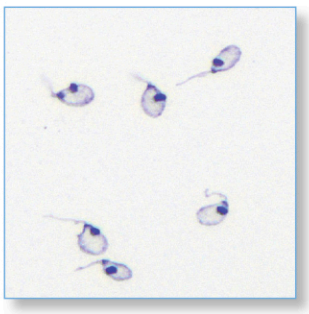
Damage to the substrate caused by moving the coverslip or by touching the substrate with a pipet tip.

Non-specific Film 39



Non-specific film caused by adsorption of serum proteins to the slide surface.

dsDNA positive 40



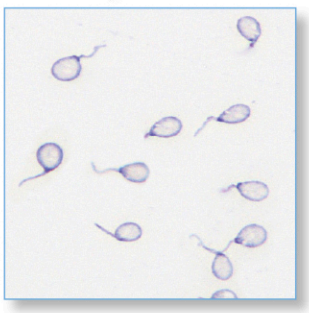
Pattern: Positive staining of the kinetoplast in the *Crithidia luciliae*

Report as: nDNA positive

Suspected antigen specificity: nDNA or dsDNA

Clinical significance: Marker antibody seen in 30–70% of SLE patients.

dsDNA negative 41

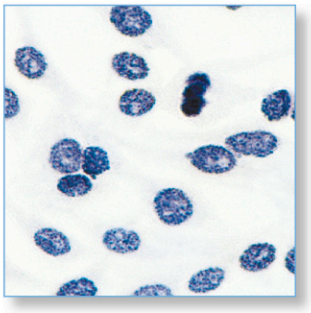


Pattern: No apparent staining of the kinetoplast in the *Crithidia luciliae*

Report as: nDNA negative

Suspected antigen specificity: None.

LEDGF 42



Report as: Homogeneous and Speckled*

Suspected antigen specificity: Lens epithelium-derived growth factor/diffuse fine speckled (LEDGF/DFS)*

Clinical significance: Unknown.

Follow-up testing: None required.

*Variability in staining has been reported with these antibodies. While this sample was positive for anti-LEDGF not all anti-LEDGF samples will demonstrate these patterns.

Kohler Illumination

Use Kohler Illumination to optimize the illumination of your sample and to reduce the visibility of the light source image. Here's how to do it:

1. Turn on the bright field light source.
2. Place a blue filter and a neutral density filter on top of the light source.
3. Place the slide on the stage and set magnification to 10x or 20x.
4. Focus the specimen.
5. Close the field diaphragm as far as possible. This is located towards the bottom of the microscope where the light source is coming from.
6. Close the condenser or iris aperture, located under the stage, until the field of view outside the field diaphragm is evenly dark.
7. Slowly turn the condenser focus knobs to bring the edges of the field diaphragm into the best focus.
8. When the edges of the diaphragm are sharply defined, the diaphragm can then be centered. Use the condenser-centering screws to center the image of the closed field diaphragm into the center of the field of view.
9. Open the field diaphragm so that the edges are just outside and beyond the field of view.
10. Open the condenser or iris aperture to introduce the proper amount of light and contrast.
11. Adjust the light intensity as necessary.

(If reading COLORZYME®, a blue filter with a neutral density filter are suggested.)

Suggested Reading

Slide Based ANA methods

Kroshinsky, D., Stone JH., Bloch DB., Sepehr A."Case records of the Massachusetts General Hospital. Case 5-2009. A 47-year-old woman with a rash and numbness and pain in the legs."N Engl J Med 2009;360(7): 711-20.

Meroni PL, Schur PH. ANA screening: an old test with new recommendations. Ann Rheum Dis. Aug 2010;69(8):1420-1422.

Colorzyme ®Method

Fritzler MJ, Wall W, Gohill J, et al. The Detection of Autoantibodies on HEp-2 Cells Using an Indirect Immunoperoxidase Kit (Colorzyme®). Diag Immunol. 1986;4:217-221

Testing Guidelines

Kavanaugh A, Tomar R, Reveille J, et al. Guidelines for clinical use of the antinuclear antibody test and tests for specific autoantibodies to nuclear antigens. Arch.Pathol.Lab.Med. 2000;124:71-81.

Tozzoli R, Bizzaro N, Tonutti E, et al. Guidelines for the laboratory use of autoantibody tests in the diagnosis and monitoring of autoimmune rheumatic diseases. Am.J.Clin.Pathol. 2002;117:316-324.

NCCLS Quality Assurance of Laboratory Tests for Autoantibodies to Nuclear Antigens: (1) Indirect Fluorescence Assay for Microscopy and (2) Microtiter Enzyme Immunoassay Methods; Approved Guidelines - Second Edition. CLSI I/LA2-A2. 2006;26(13).

HEp-2000®

Keech CL, McCluskey J, Gordon TP. Transfection and overexpression of the human 60-kDa Ro/SS-A autoantigen in HEp-2 cells. Clin.Immunol.Immunopathol. 1994;73:146-151.

Keech CL, Howarth S, Coates, et al. Rapid and sensitive detection of anti-Ro (SS-A) antibodies by indirect immunofluorescence of 60kDa Ro HEp-2 transfectants. Pathology. 1996;28:54-57.

Fritzler MJ, Miller BJ. Detection of autoantibodies to SS-A/Ro by indirect immunofluorescence using a transfected and overexpressed human 60 kD Ro autoantigen in HEp-2 cells. J.Clin.Lab.Anal. 1995;9:218-224.

Pollock W, Toh BH. Routine immunofluorescence detection of Ro/SS-A autoantibody using HEp-2 cells transfected with human 60 kDa Ro/SS-A. J.Clin.Pathol. 1999;52:684-687.

Bossuyt X, Meurs L, Mewis A, et al. Screening for autoantibodies to SS-A/Ro by indirect immunofluorescence using HEp-2000® cells. Ann Clin Biochem. 2000;37:216-219.

Reiff A, Haubruck H, Amos MD. Evaluation of a recombinant antigen enzyme-linked immunosorbent assay (ELISA) in the diagnostics of antinuclear antibodies (ANA) in children with rheumatic disorders. Clinical Rheumatology. May 2002;21(2):103-107.

Arbuckle, MR., McClain MT., Rubertone MV., et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. New England Journal of Medicine 2003. 349(16): 1526-1533.

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